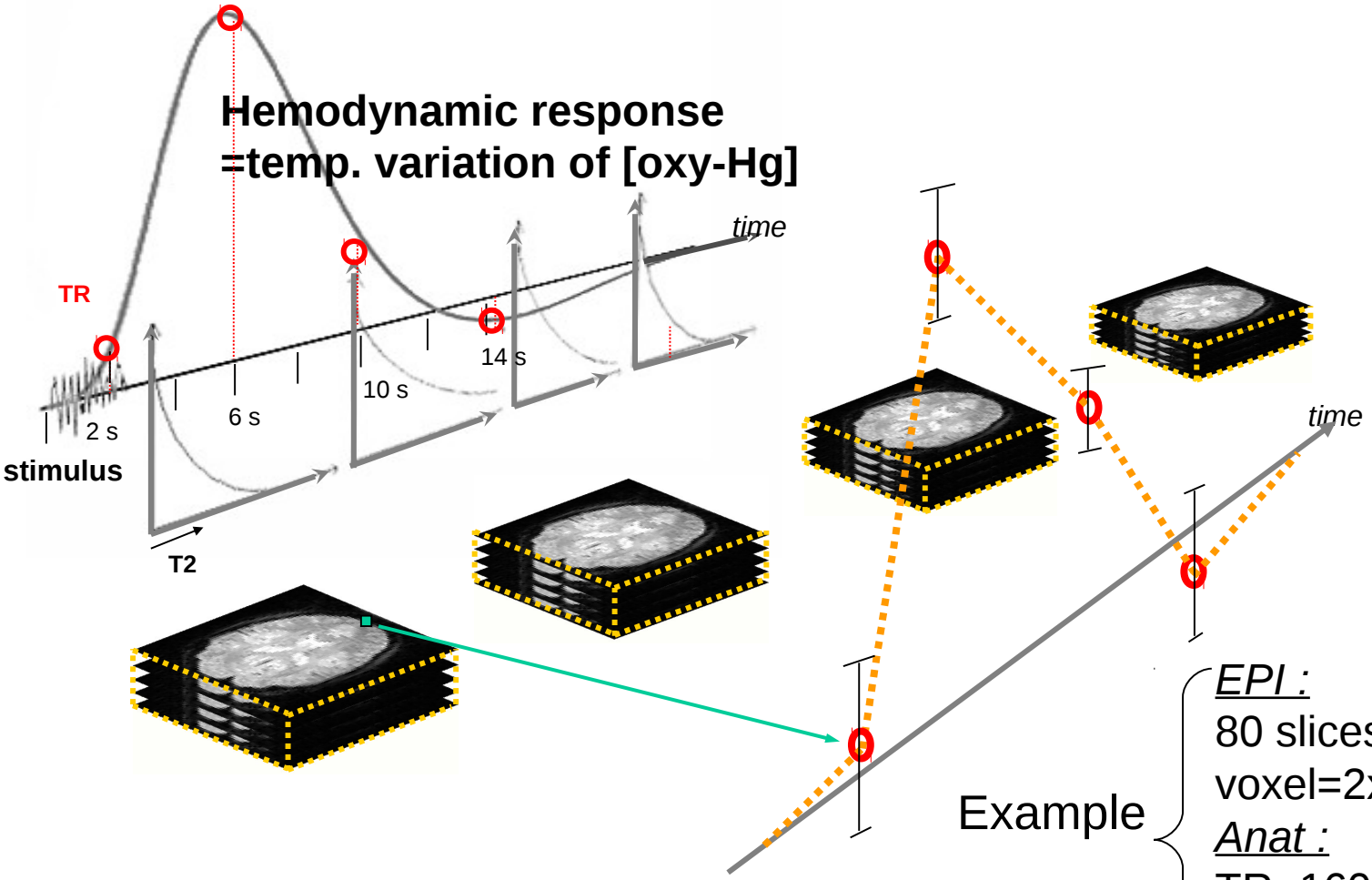
Part III Machine Learning for functional Neuroimaging

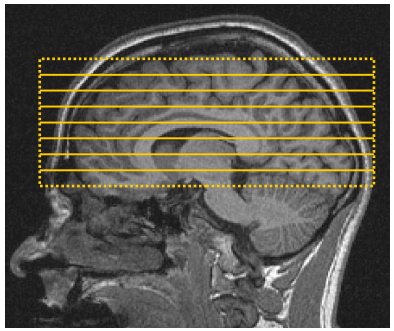
Outline

- The standard *multivariate pattern analysis* setting
- Identification of predictive features
- Mapping *and* predicting: Spatial Regularization
- Toward big data analysis

Introduction: functional Magnetic Resonance Imaging

The BOLD response



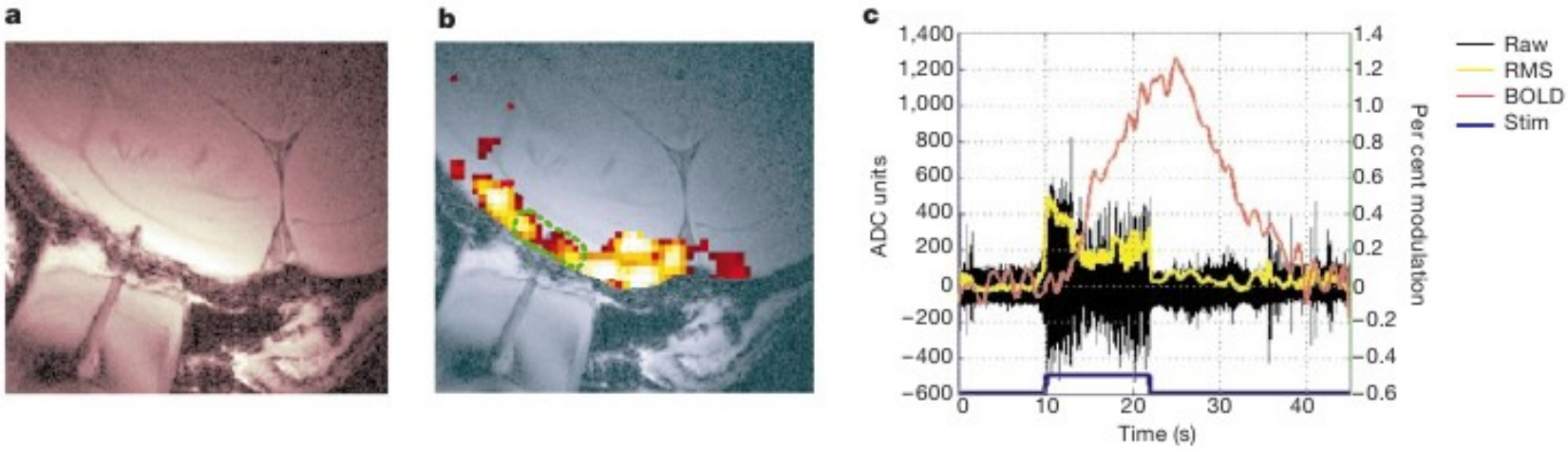


Example

EPI :
80 slices, TR=2000 ms, TE=30ms,
voxel=2x2x2mm, 96x96 matrix
Anat :
TR=1600ms, FOV=256x256mm2,
256X256 matrix, 192 slices
Slice thickness 1mm

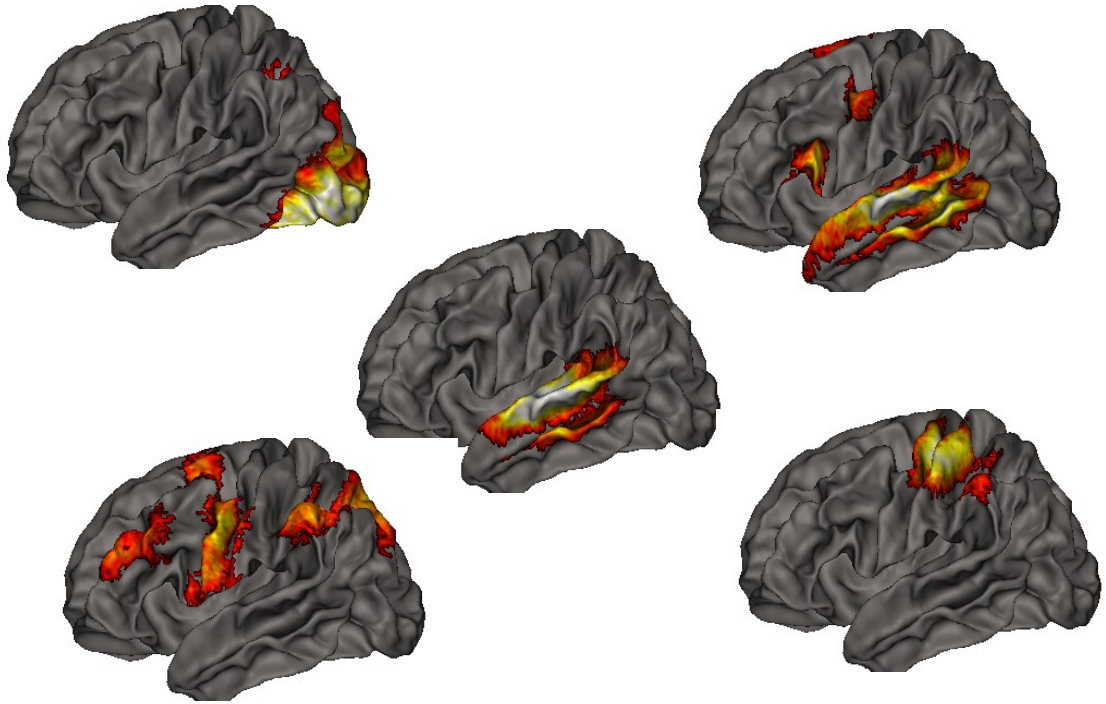
Human BOLD imaging

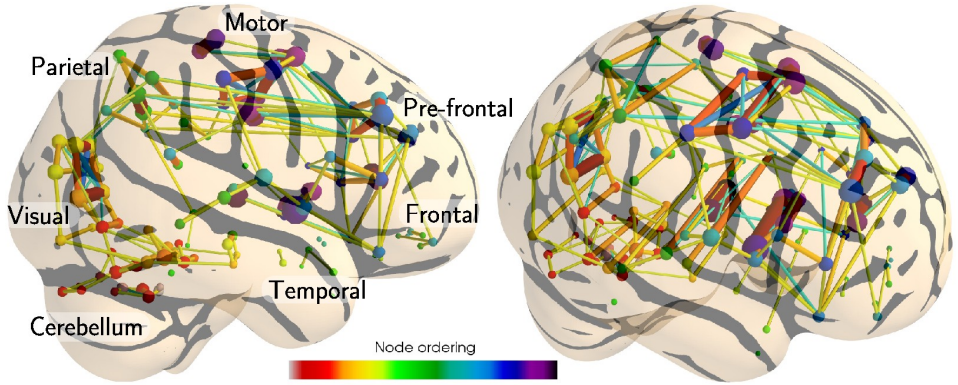
- BOLD response approximately linear in the stimulus function
  - Application of simple linear model for data analysis [Friston et al. 1995]
- BOLD signal highly correlated with LFPs [Logothetis et al. Nature 2001]
- High spatial accuracy (~2mm) [Ugurbil et al. NeuroImage 2007]
- Poor temporal resolution, no consensual model on the signal



Human BOLD imaging

- fMRI used intensively to map cognitive functions in the human brain.
- BOLD correlations across regions used to study functional connectivity
- Combining the signals across regions can be used to fit accurately the subject's behavior

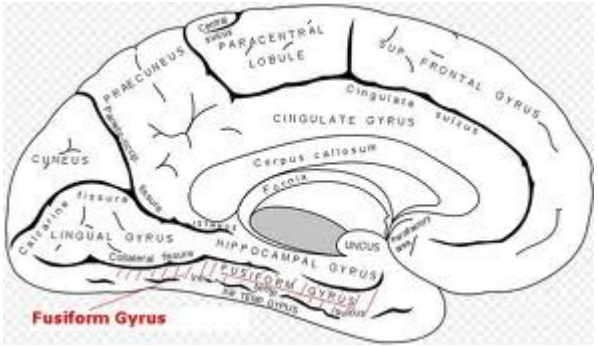




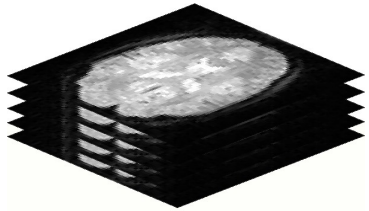
Machine learning for cognitive neuroimaging : decoding and encoding models

- Statistical analysis of fMRI data
- encoding models: mapping stimulus features to brain activations
- decoding models: predicting behavior from activation maps / “Vanilla MVPA”

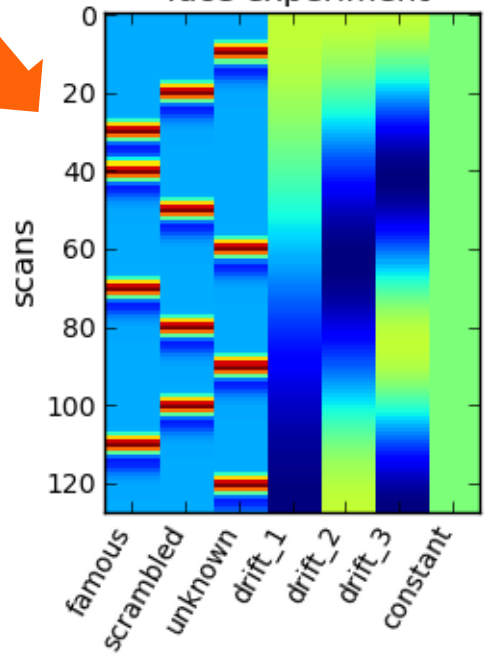
fMRI data from acquisition to analysis

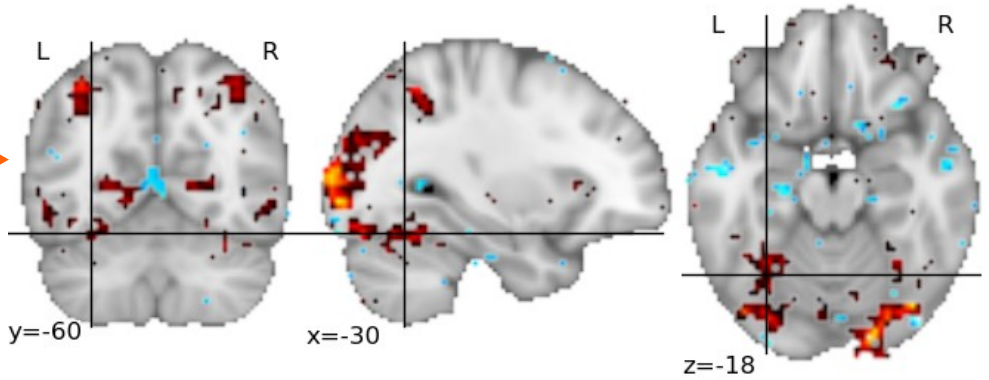


Complex metabolic pathway



Block design matrix face experiment





Statistical inference

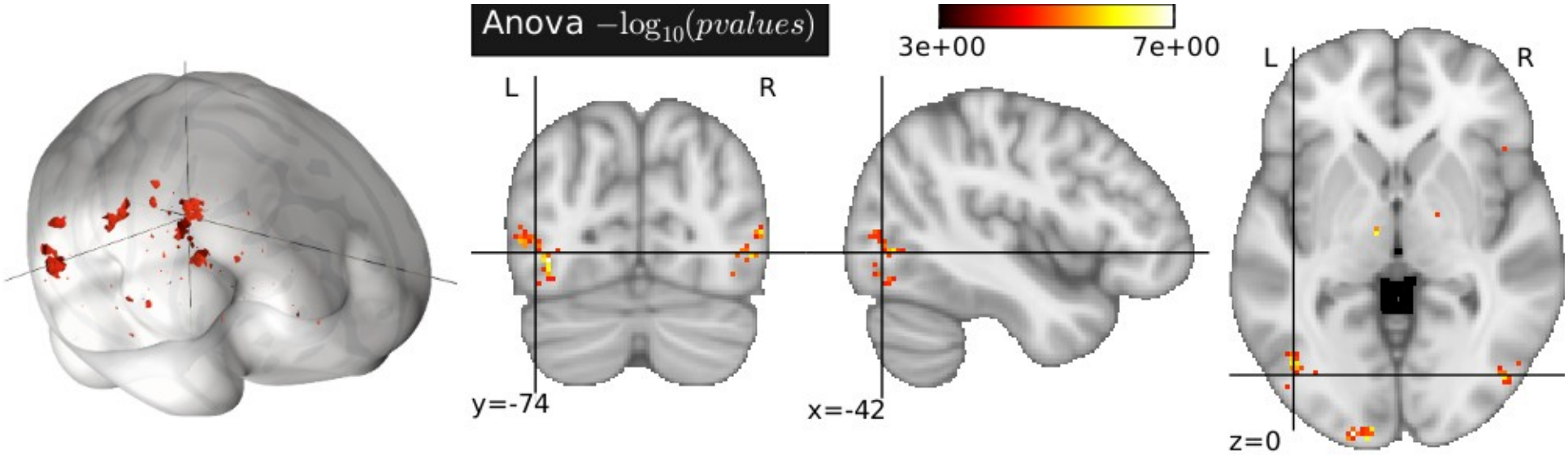
Question 1 : Is there any effect of the paradigm on the data ?

“omnibus test”

Can I discriminate between the two conditions ?

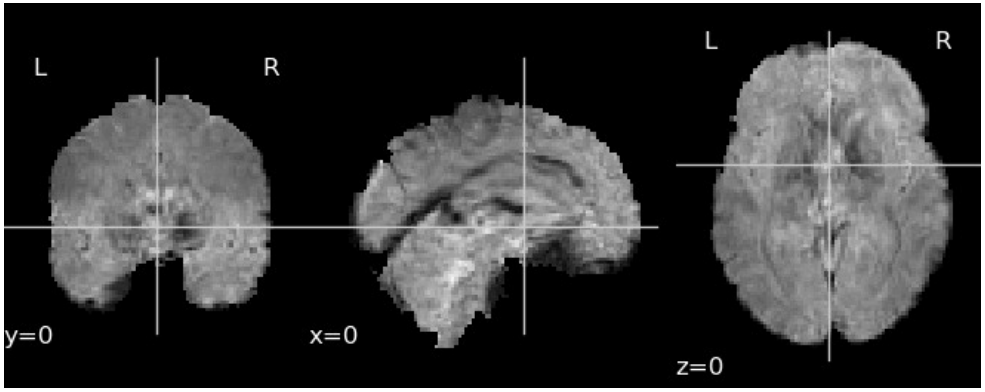
Question 2 : What regions actually display an effect of the paradigm ?

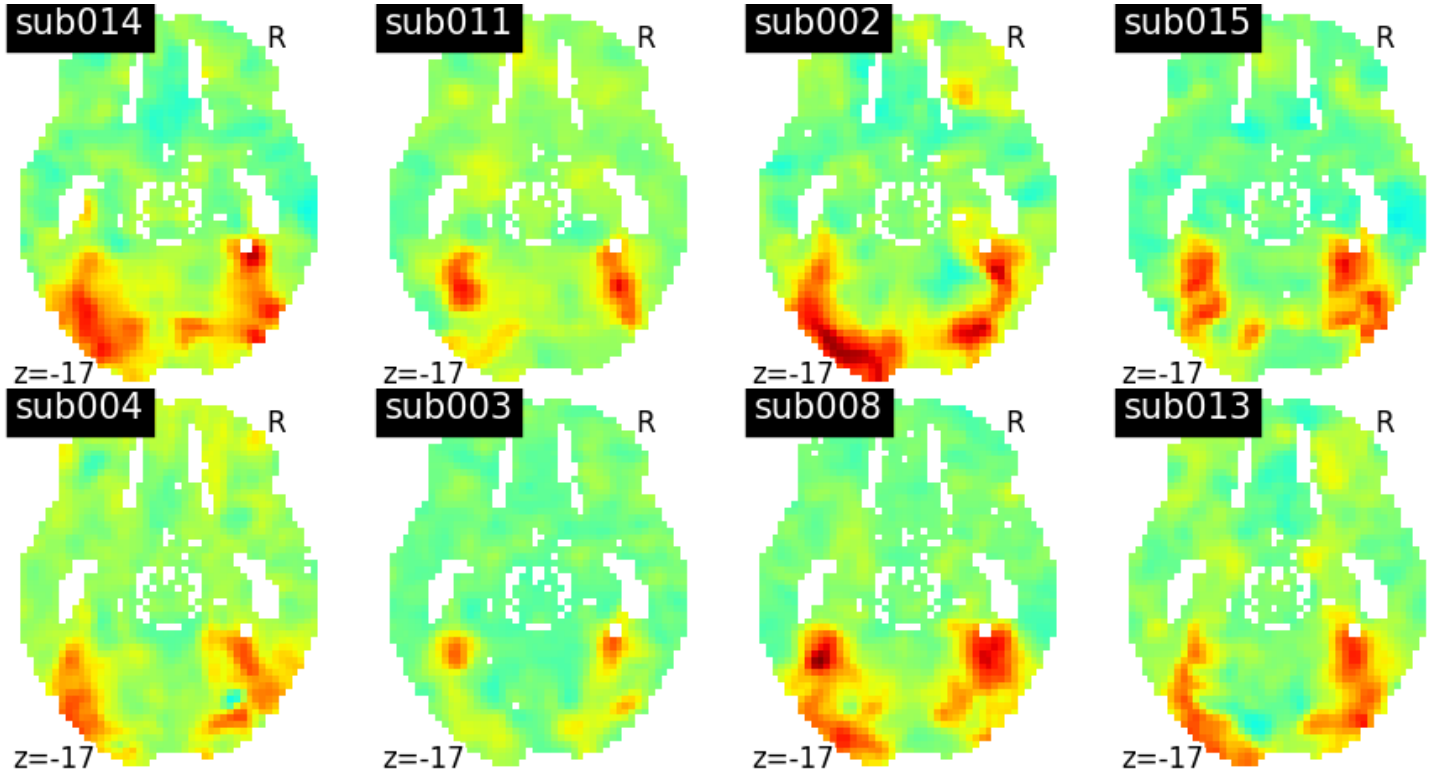
What are the relevant features ?



Common problems

- Low SNR
- High variability between subjects
- Small sample sizes





Common problems: sample size

Nature Reviews Neuroscience | AOP, published online 10 April 2013; doi:10.1038/nrn3475

nature REVIEWS

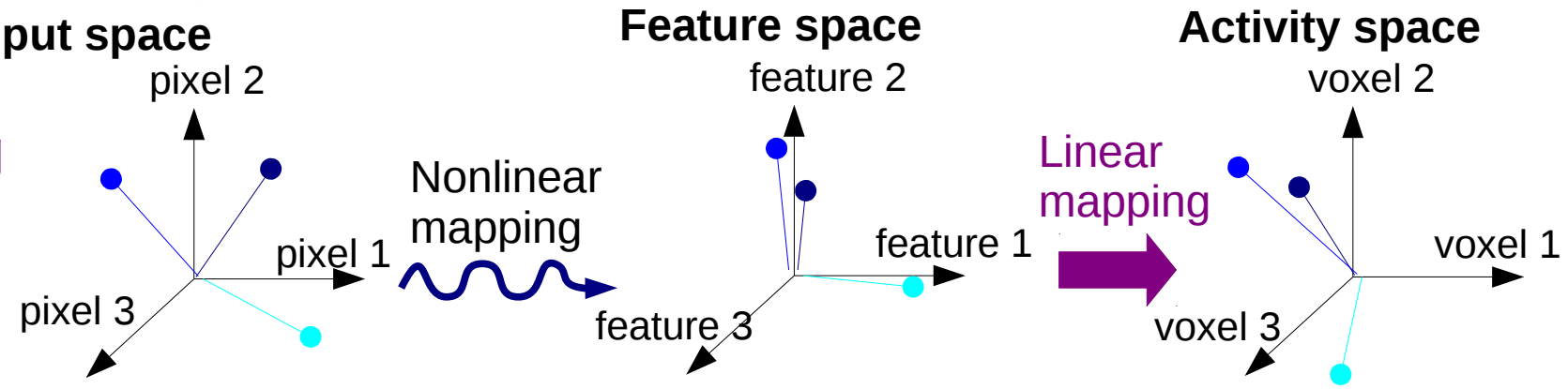
Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button[1,2], John P. A. Ioannidis[3], Claire Mokrysz[1], Brian A. Nosek[4], Jonathan Flint[5], Emma S. J. Robinson[6] and Marcus R. Munafò[1]

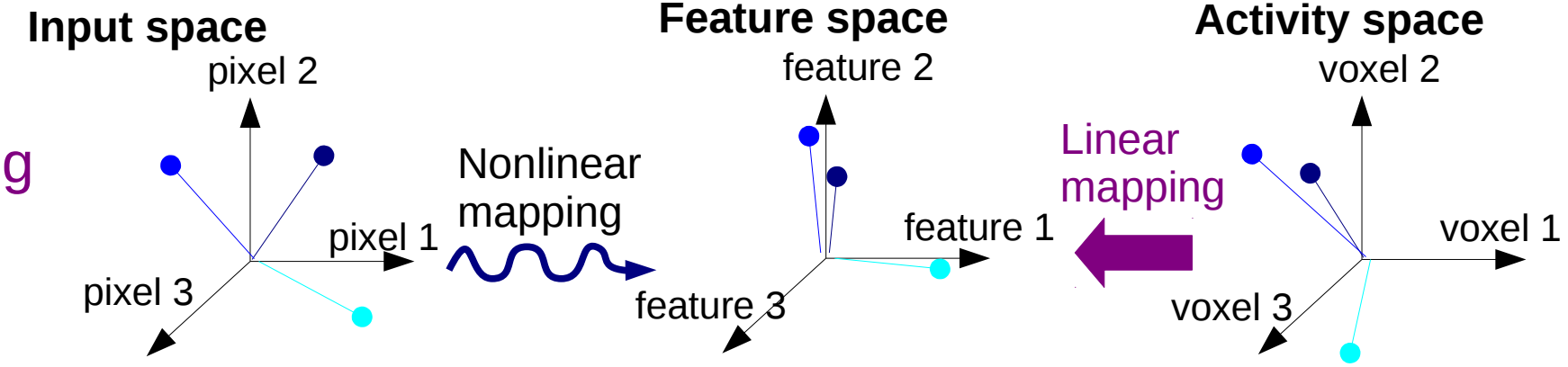
Small number of subjects → Lack of power
- → many false negatives
- → results are weakly informative
- → reported effects are inflated

All these issues are present in MVPA
Reflected in classifier instability, variable performance

encoding model



decoding model



[Naselaris et al. NeuroImage 2009]

Encoding visual stimuli

- Activation patterns encode some information about the stimuli
- Population receptive field
  - Location-specific (depends on where you are on the cortex)
  - Feature-related (position, contrast, speed, color...)

$$\mathbf{y} = \phi(\mathbf{X})\beta + \varepsilon$$

e.g. ϕ = wavelet transform

Signal in a voxel

Input stimulus

Voxel-specific response

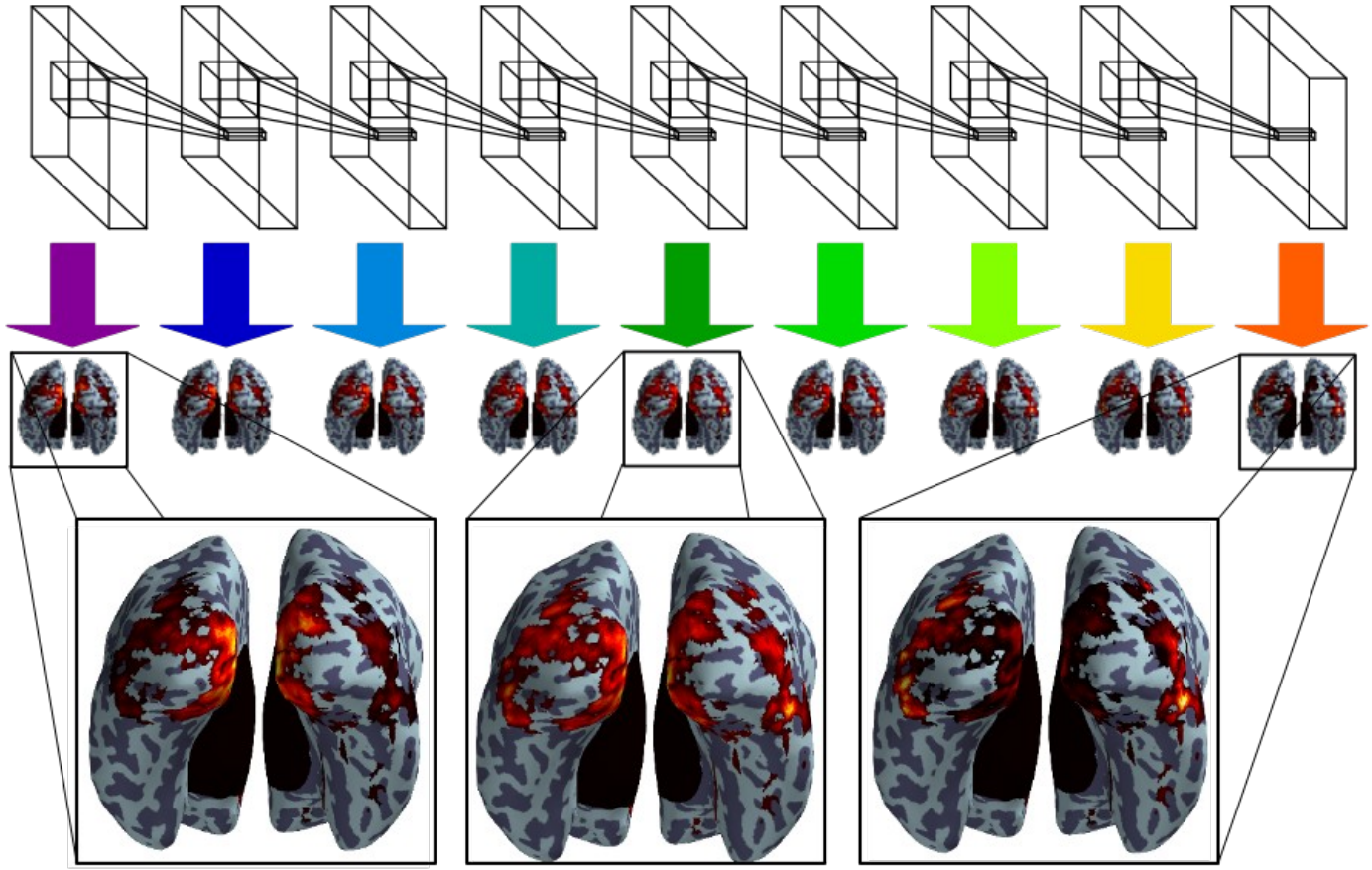
Encoding visual stimuli

Create Features

Convolution model: Feedfoward model of vision for object recognition

Comparison with fMRI

How well are brain regions explained by the features ?

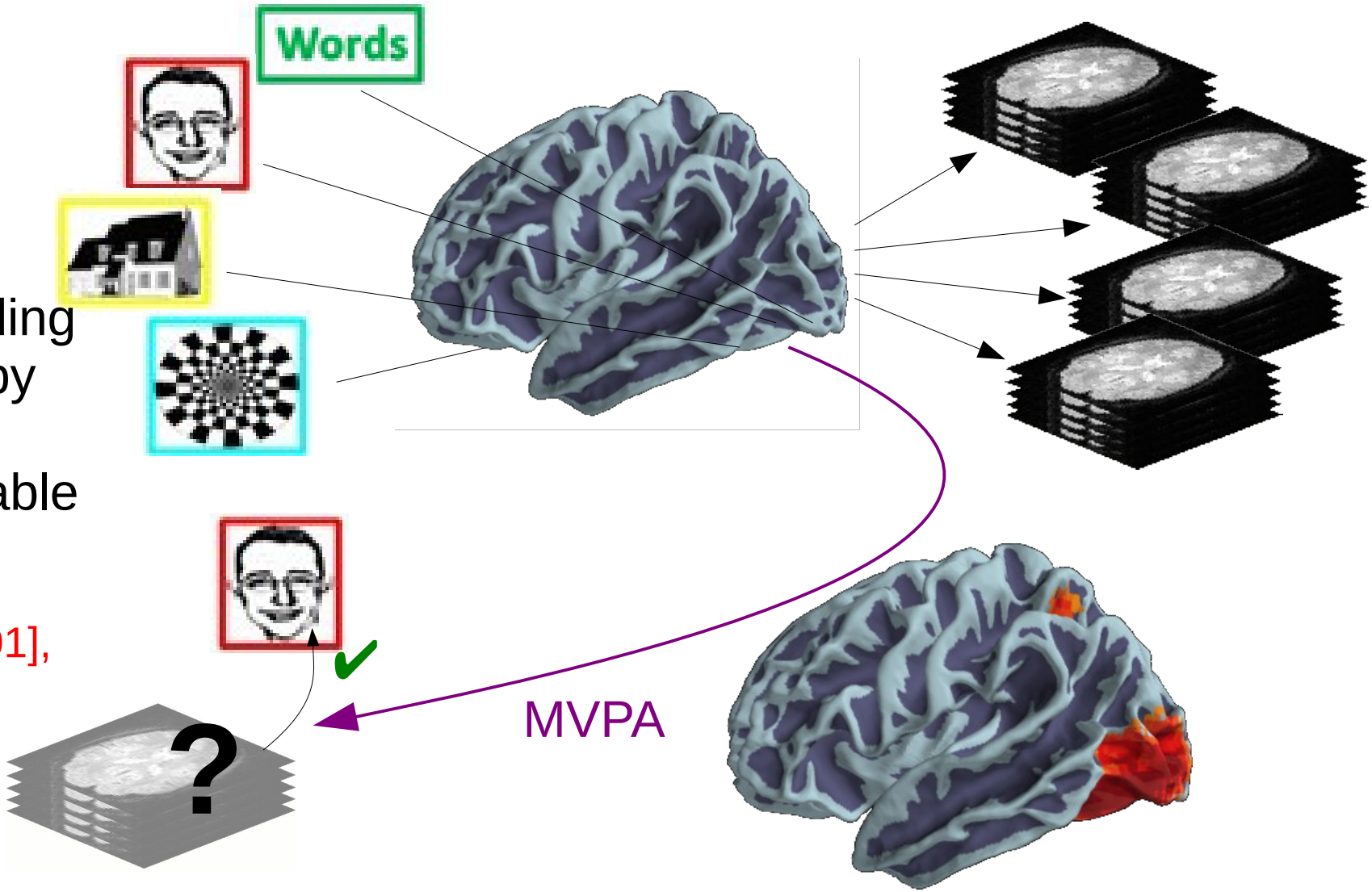


[Eickenberg et al. submitted]

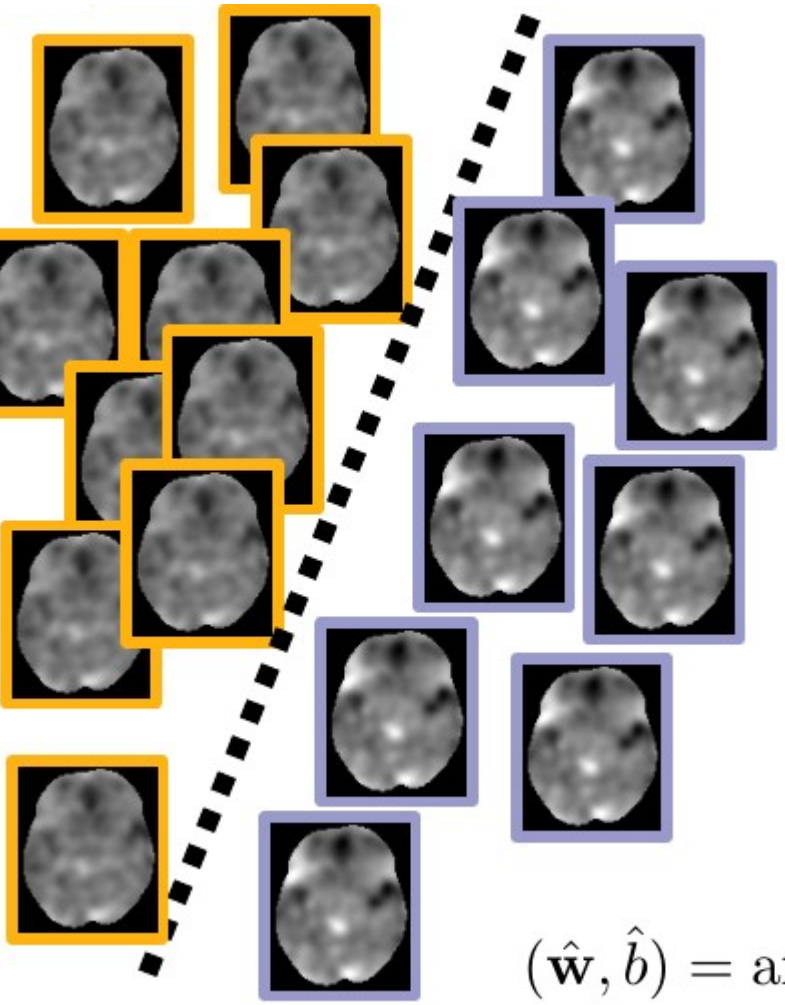
FMRI decoding: Reverse inference

Aims at decoding brain activity by predicting a cognitive variable

[Dehaene et al. 1998],
[Haxby et al. 2001],
[Cox et al. 2003]



Training classifiers for FMRI data



Main setting:
features = the voxel-level BOLD contrast
Target = conditions (discrete)

- Given x in R^p, (fMRI volume with p voxels), predict a label y in {-1, 1}
  i.e. ▮ or ▮

  or better the class probability
  Proba(x = 1|y)

$$(\hat{\mathbf{w}}, \hat{b}) = \operatorname{argmin}_{\mathbf{w},b} \sum_{i=1}^{n} \log\left(1 + \exp\left(-x_i(y_i\mathbf{w} + b)\right)\right) + \alpha\|\mathbf{w}\|_2^2$$

Evaluation of the decoding

Prediction accuracy

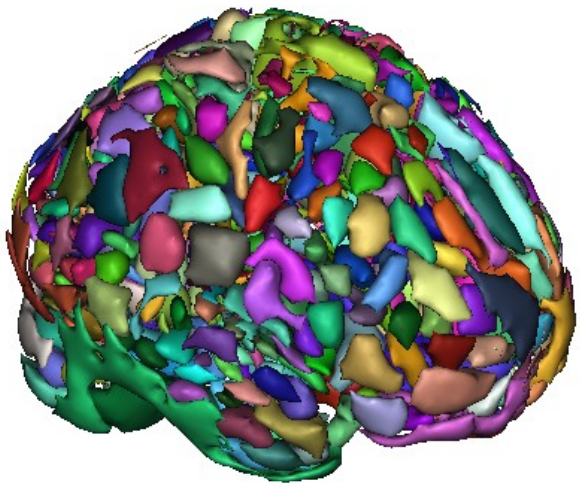
→ Quantify the **amount of information** shared by the pattern and y.

Layout of the resulting maps of weights:
The discriminative pattern characterizes brain processes / biomarkers

Common hypothesis = segregation into functionally specific territories

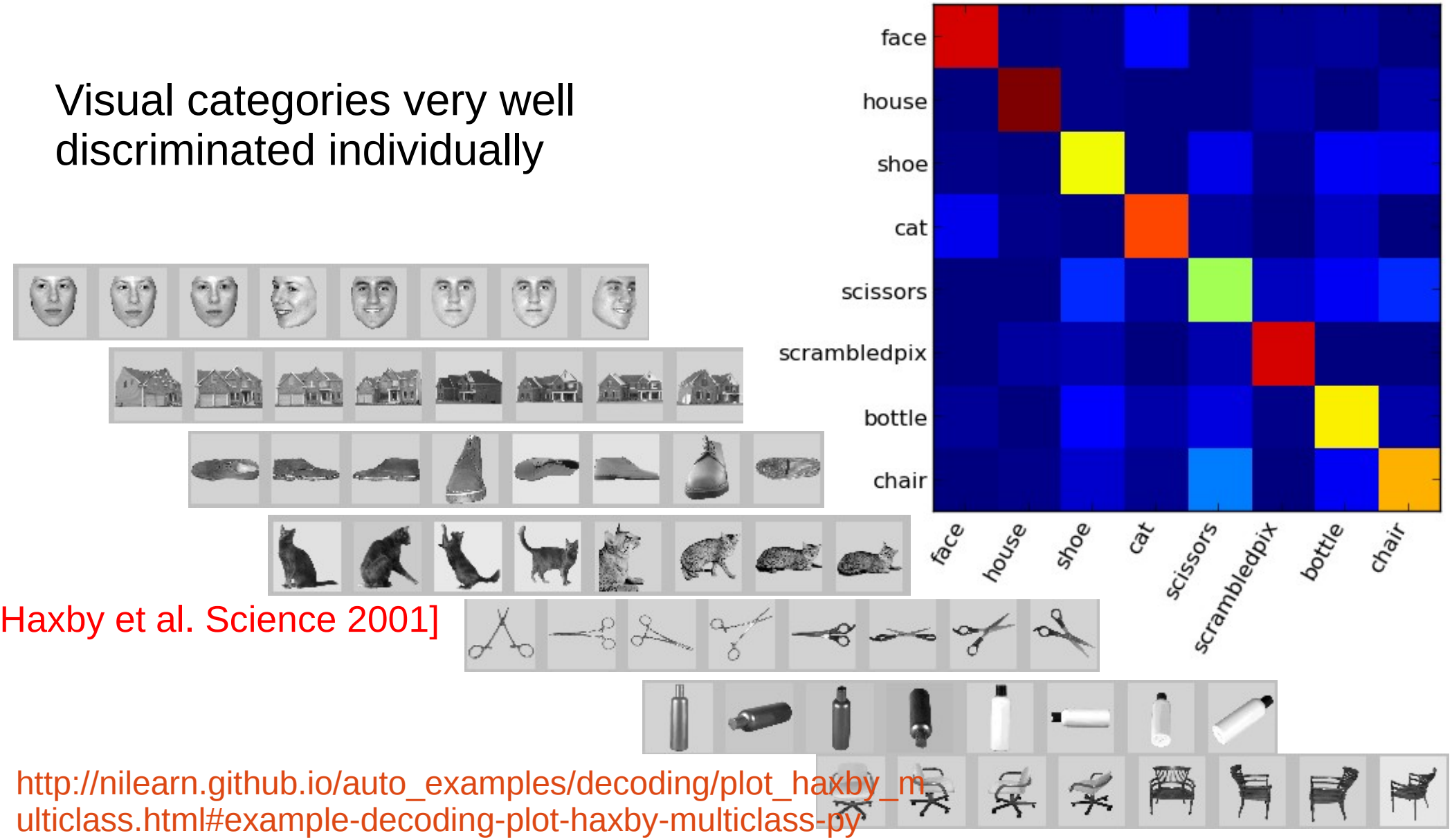
→ **sparse**: few relevant regions implied

→ **compact structure**: grouping into connected clusters.



Decoding visual categories

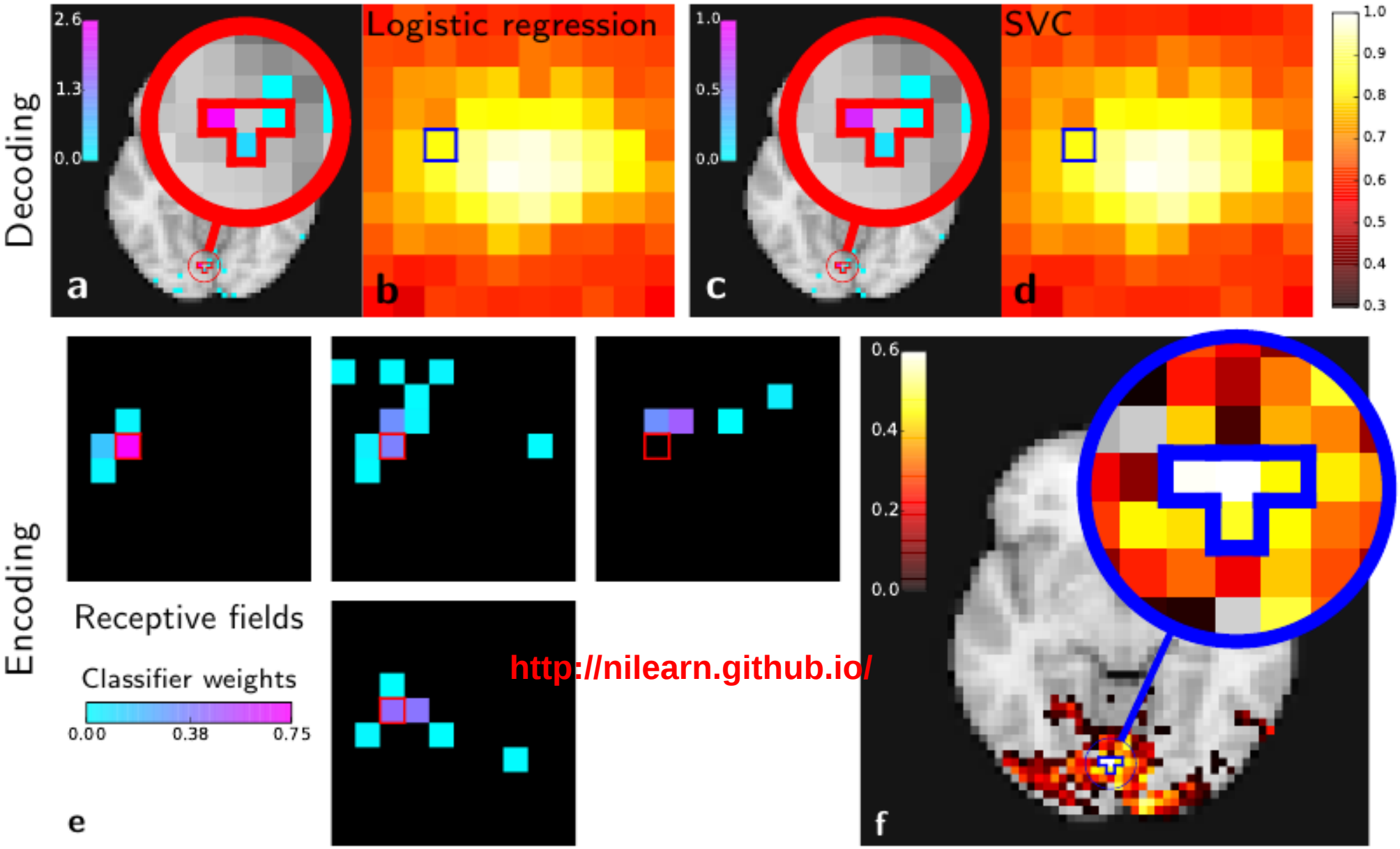
Visual categories very well discriminated individually



[Haxby et al. Science 2001]

http://nilearn.github.io/auto_examples/decoding/plot_haxby_multiclass.html#example-decoding-plot-haxby-multiclass-py

Encoding and decoding: do it yourself !



More topics

- Separate GLM approach improves classification accuracy [Mumford et al. NIMG 2012]
- Data-driven hrf estimation alos yields more accurate models [Pedregosa et al. Nimg 2014]

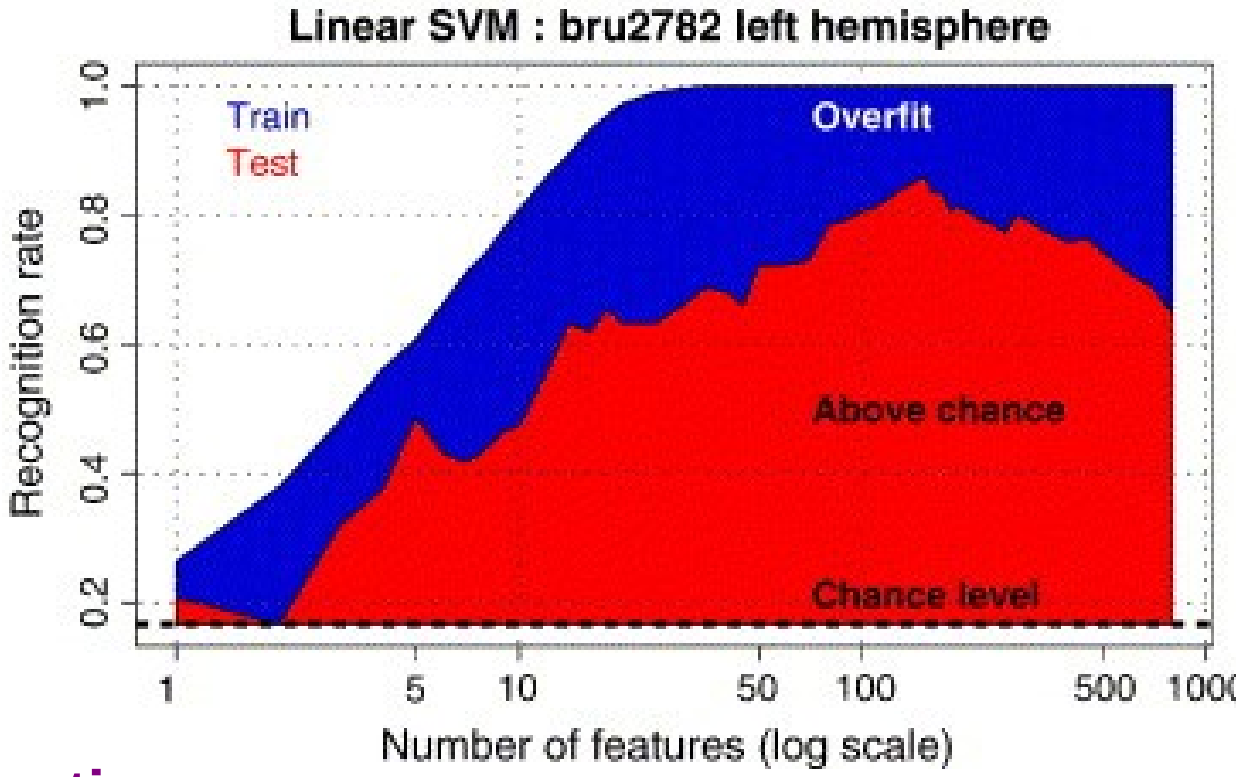
Region selection and Identification

- Spatial models in MVPA
- Identification : Recover the truly associated features
- Ill-posedness of the problem. Current solutions.

Curse of dimensionality in MVPA

Problem: p ≫ n

- Overfit the noise on the training data



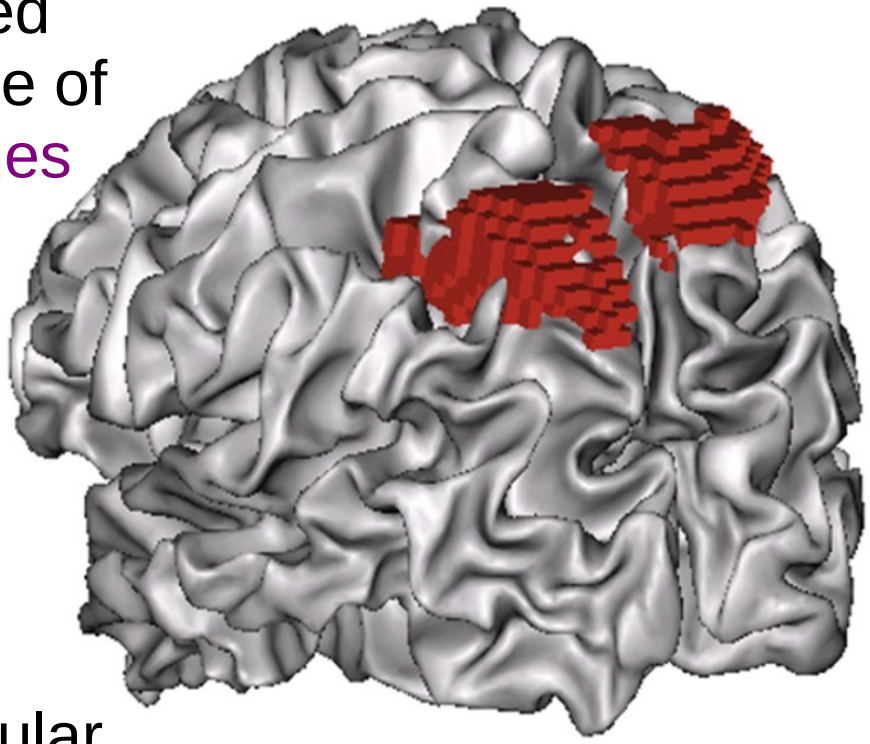
Solutions

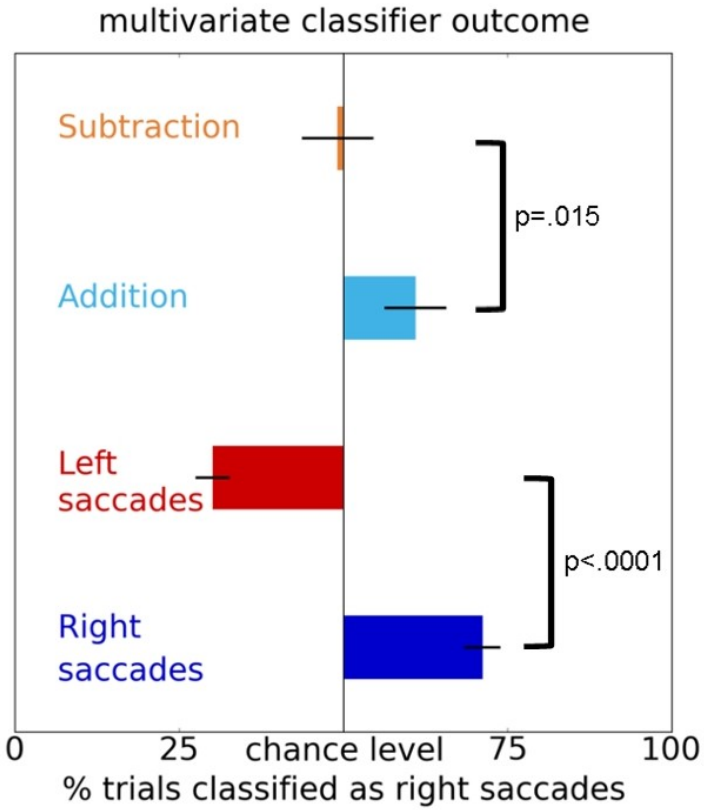
- **Prior region selection**
  - prior-bound result
- **Data-driven feature selection**
  - Univariate methods (Anova)
  - Multivariate methods
- **Regularization** (e.g. Lasso, Elastic net)
  - Shrink w according to your prior

ROI-based analysis

Example:

- Selection of results involved in performance of ocular saccades
- Succesful prediction of mental arithmetics
- Same neural populations involved in ocular saccades and arithmetics ?



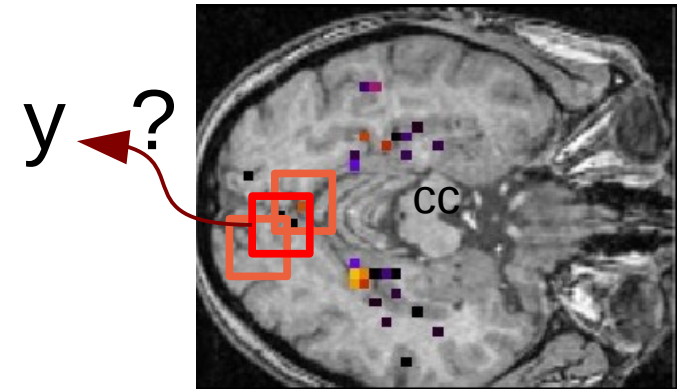


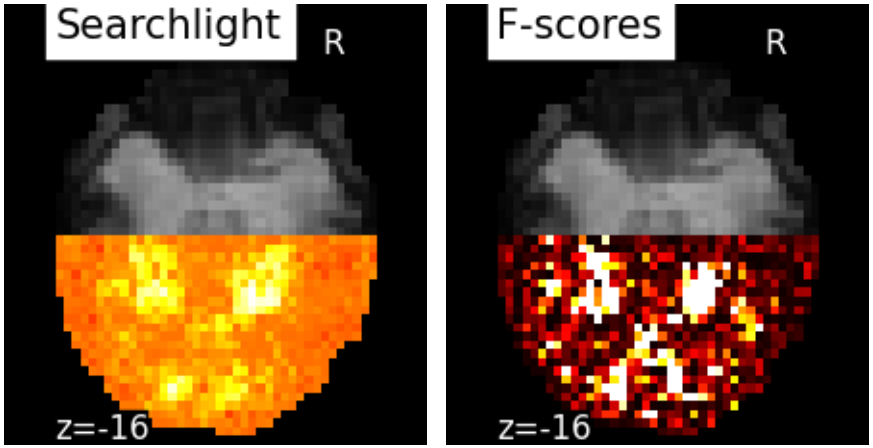
[Knops et al., 2009]

The searchlight method

[Kriegeskorte et al. PNAS 2006]

- Prediction based on a small group of neighboring voxels
- Change the region location
- Obtain a map of statistical association





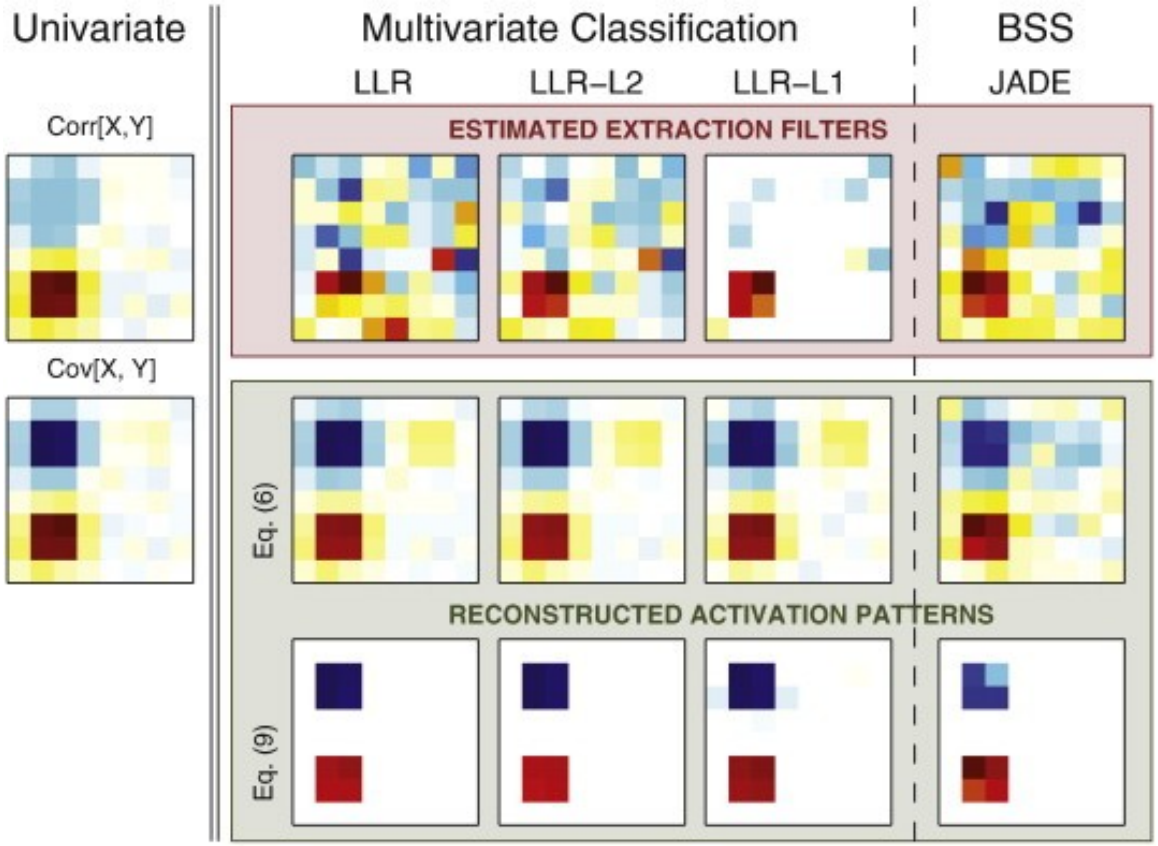
Drawbacks:
- Cost (loop over voxels + permutation testing)
- Advantage wrt standard brain mapping ?

(Non-)identifiability of the model $W = W_{true}$?

$$\hat{\mathbf{w}} = \text{argmin}_{\mathbf{w}} \mathcal{L}(\mathbf{y}, \mathbf{X}, \mathbf{w}) + \alpha \mathcal{R}(\mathbf{w})$$

- [Haufe et al. Neuroimage 2013] In decoding, you don't recover the true pattern but a **filter**
- The encoding model violates the conditions for good reconstruction [Varoquaux et al. 2012]
- Better support recovery by introducing relevant priors on the decoder [Varoquaux et al. 2012]
  - Sparsity
  - Block structure

Non-identifiability of the model ?



✗ MVPA **cannot** recover the true sources ;

➔ aims at finding a good discriminative model (“filters”)

➔ not at estimating the signal.

✗ A correction taking covariance structure is necessary...

✔ … but you cannot estimate the signal/noise covariance properly !

✔ However, this can be improved by choosing relevant priors

[Haufe et al. NIMG 2013]

Recovery...

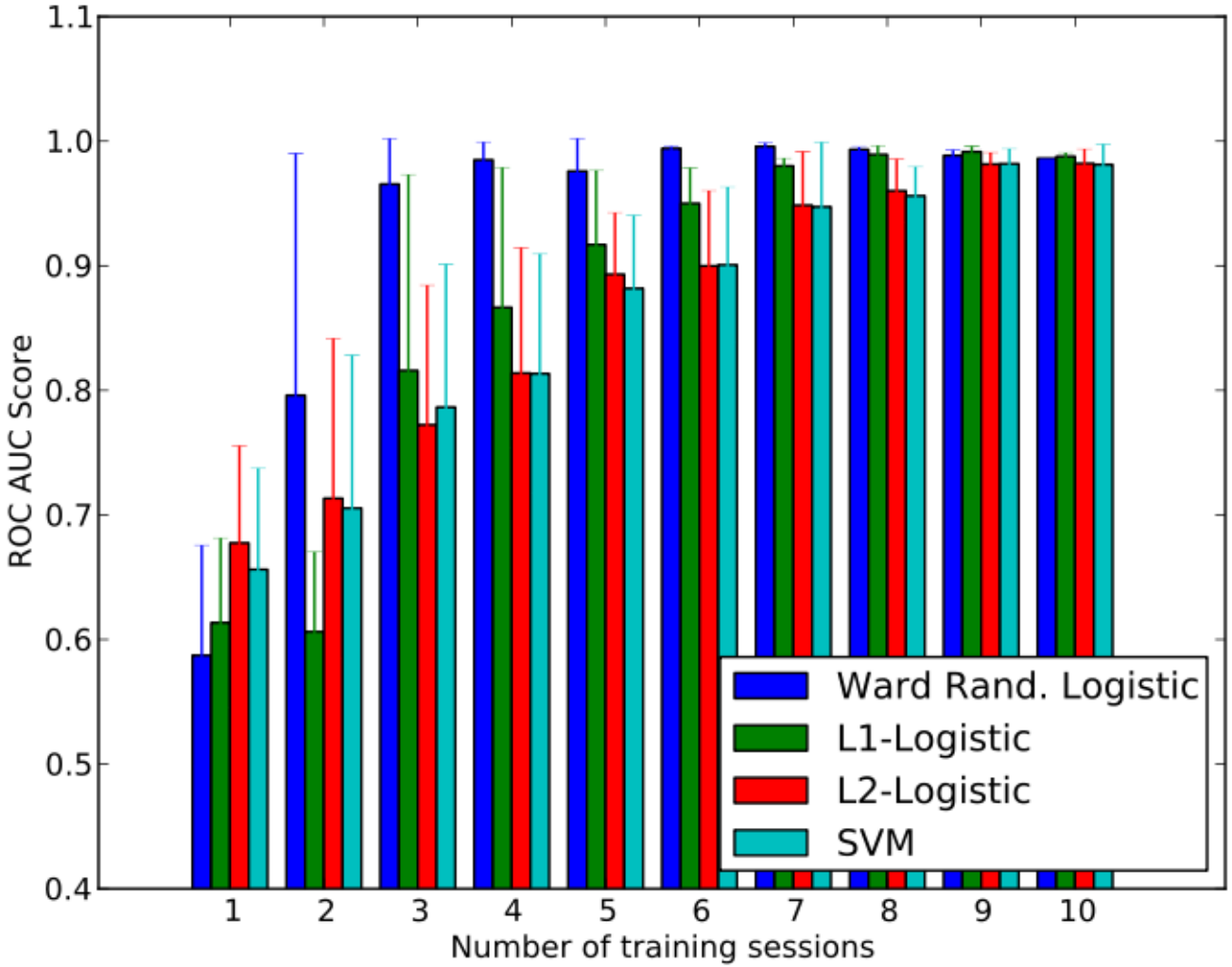
- **Compressive sensing:**
  - detection of k signals out of p (voxels)
  - with only n observations << k
  - **Problem: neuroimaging data are correlated (spatially)**
    - Violate *Restricted Isometry property.*

$$\exists \delta \in [0,1] : \forall \mathbf{w} \in \mathbb{R}^p, (1-\delta)\|\mathbf{w}\| \leq \|\mathbf{X}\mathbf{w}\| \leq (1+\delta)\|\mathbf{w}\|$$

For **any** submatrix X of the neuroimaging data matrix

How to measure the recovery of the set of regions ?
How to improve recovery?

Measuring recovery by subsampling



[Haxby Science 2001] dataset:

Trying to discriminate faces vs houses: level of performance achieved with limited number of samples

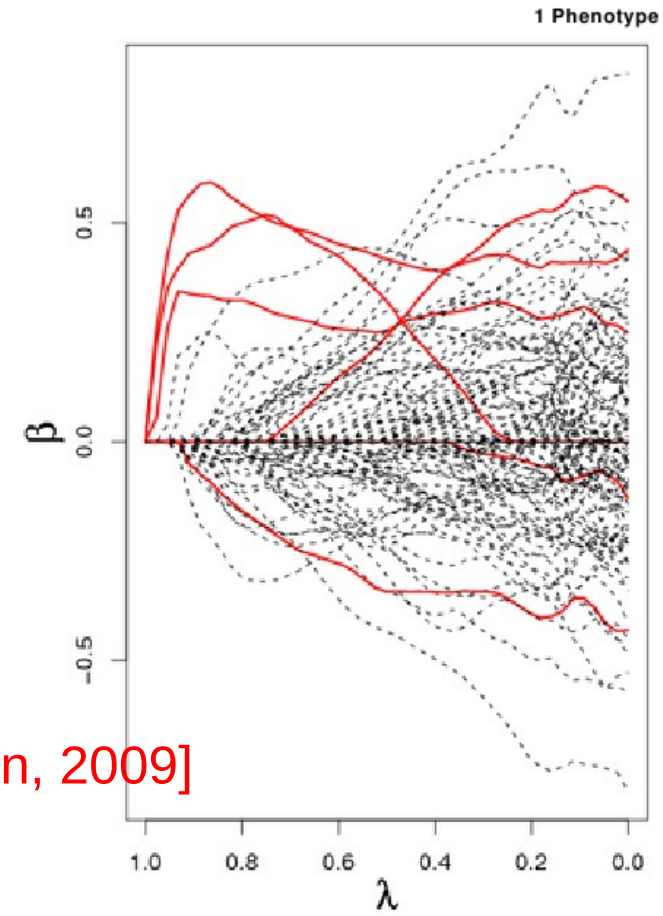
Solution: bagging to better identify

$$\hat{\mathbf{w}}^{lasso} = \text{argmin}_{\mathbf{w}\in\mathbb{R}^p} \|y - \mathbf{X}\mathbf{w}\|^2 + \alpha\|\mathbf{w}\|_1$$

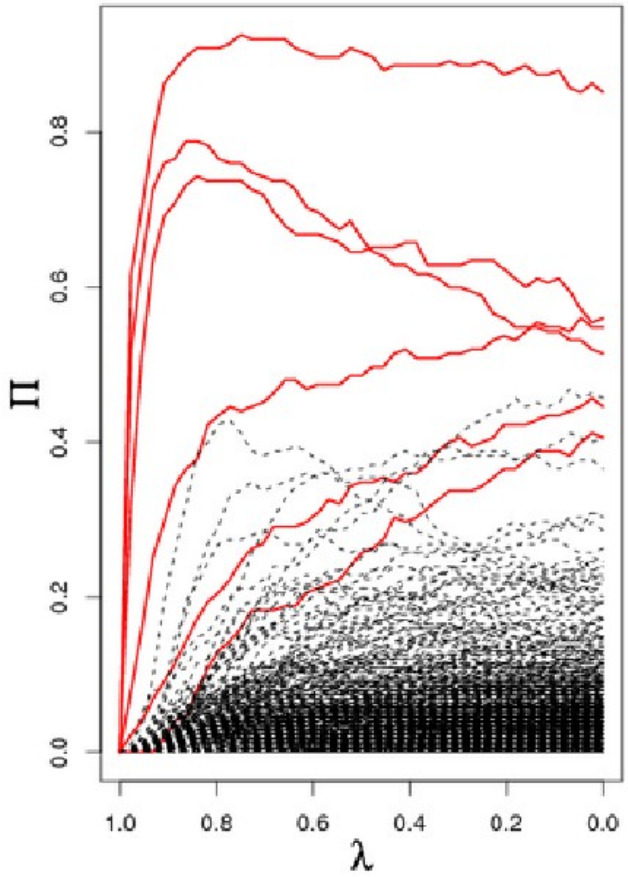
- Stability selection = randomization of the features + bootstrap on the samples
- Improved feature recovery... for **few, weakly correlated** features

[Meinshausen and Bühlman, 2009]

Lasso path



stability path of Lasso



Hierarchical clustering and randomized selection

Cluster-based stability selection algorithm

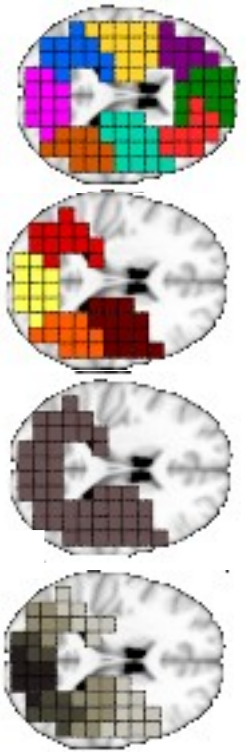
(1) **Loop**: randomly perturb the data

(2) Ward agglomeration to form q features

(3) sparse linear model on reduced features

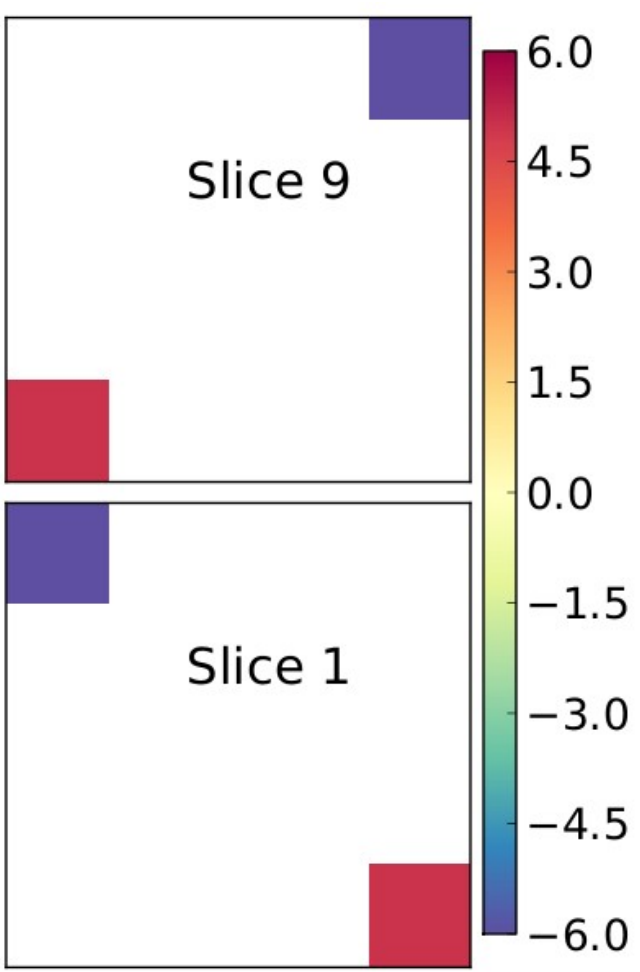
(4) accumulate non-zero features

(5) threshold map of selection counts

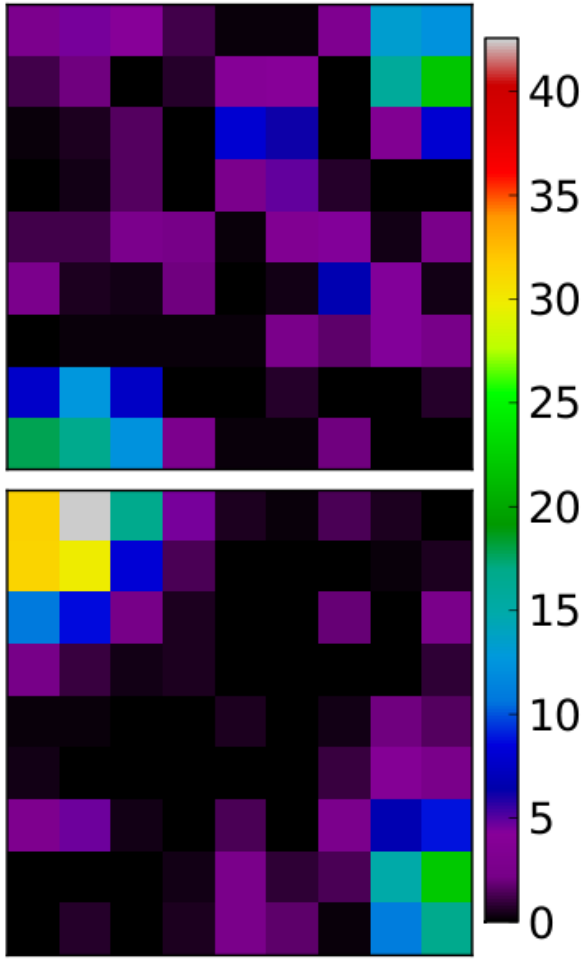


[Gramfort et al. MLINI 2011]

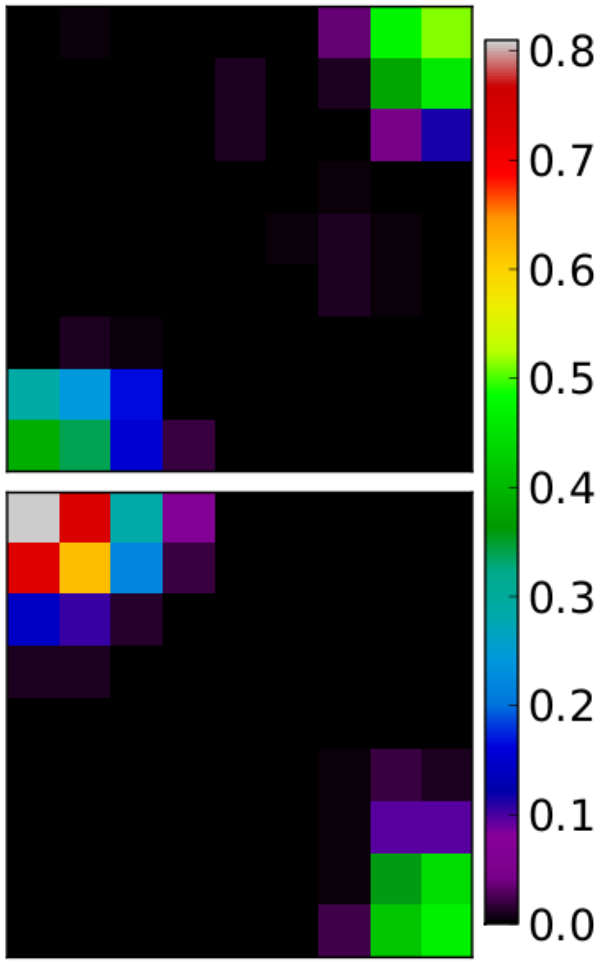
Simulation study



Ground truth



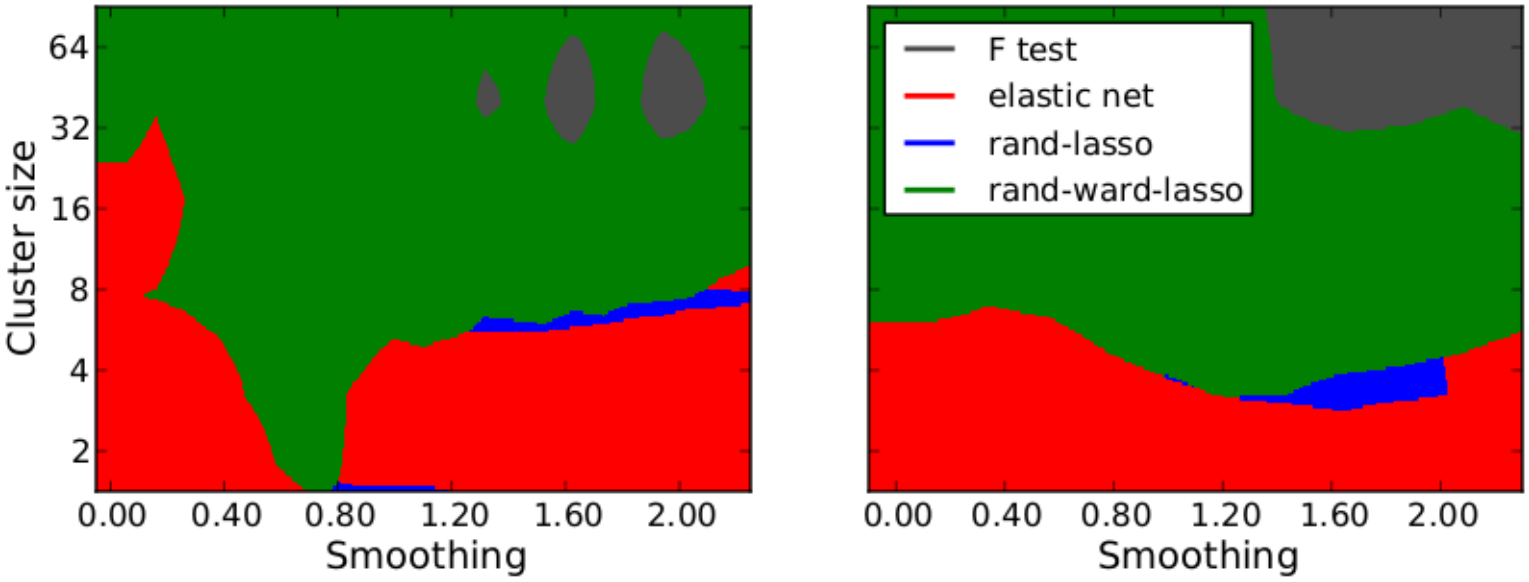
F test



Randomized Ward logistic

The best approach for feature recovery depends on the problem

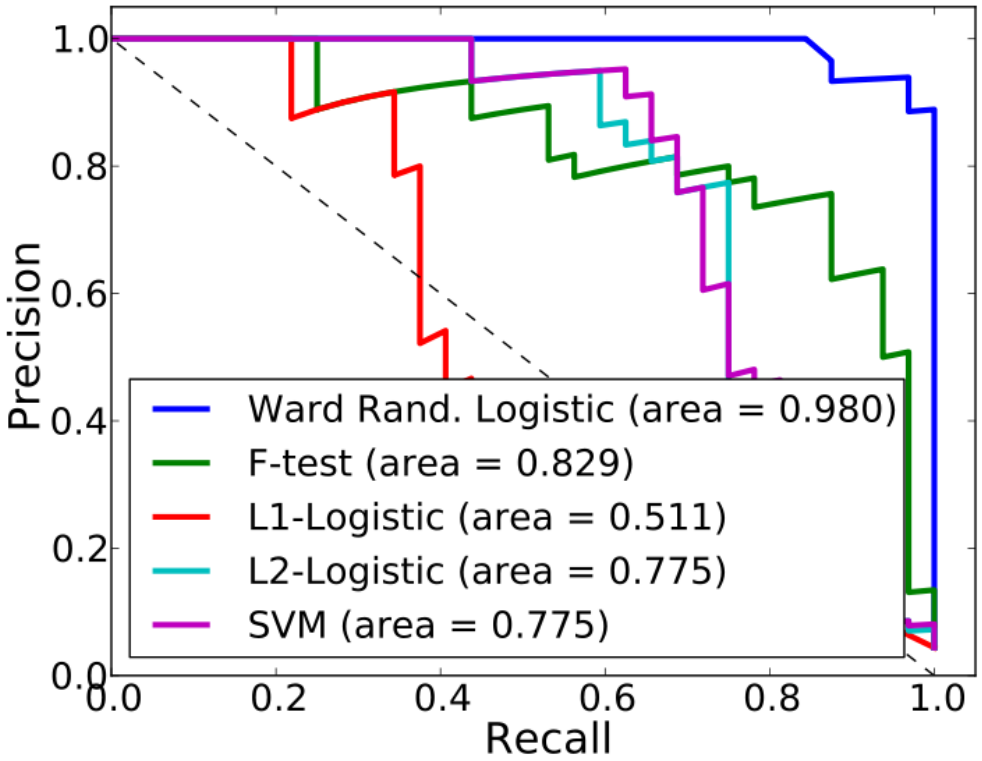
- The response depends on the characteristics of the problem: **smoothness** (coupling between signal and noise) and **clustering** (redundancy of features)



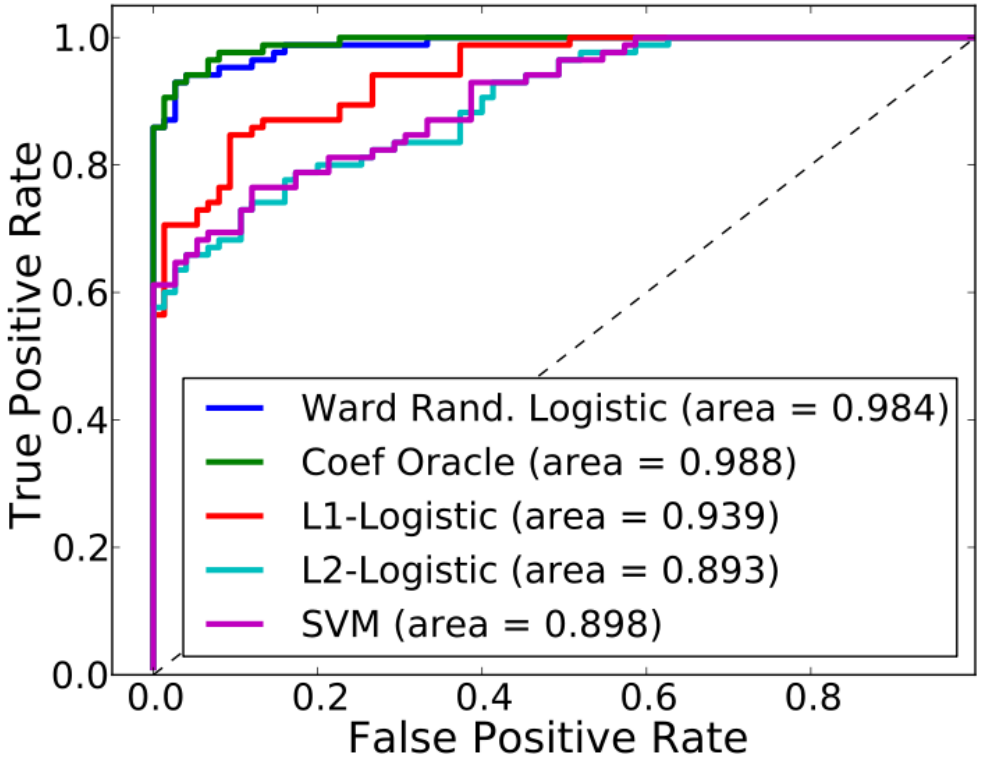
128 samples 256 samples

[Varoquaux et al. ICML 2012]

Simulation study



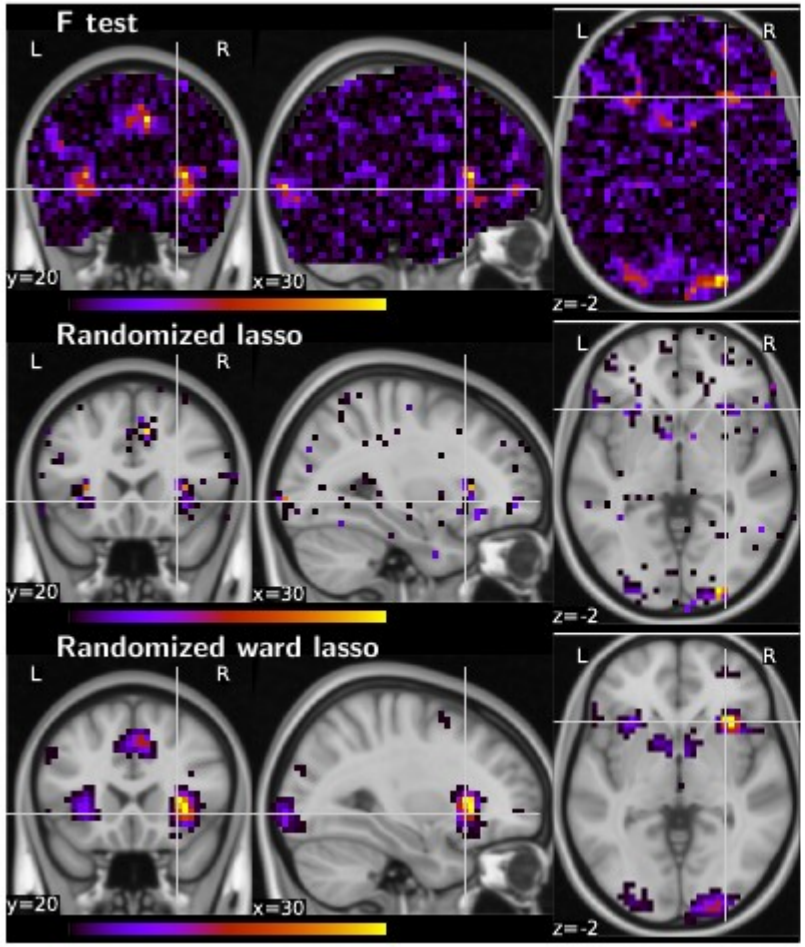
Identification accuracy



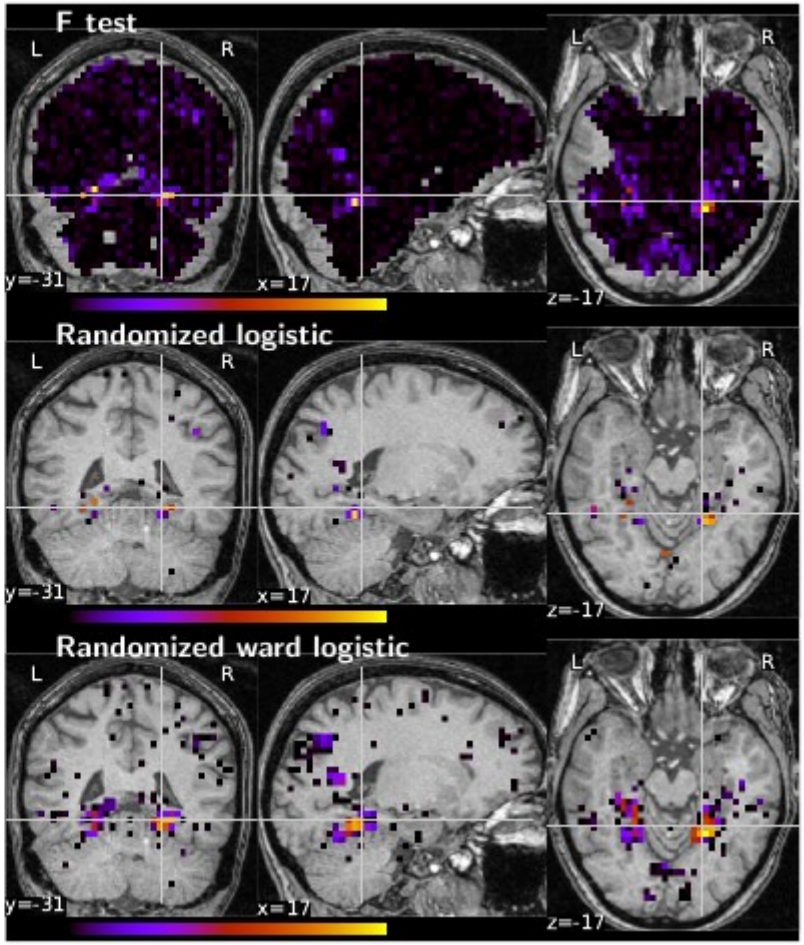
Prediction accuracy

Improves both prediction and identification !

Examples on real data



Regression task
[Jimura et al. 2011]



Classification task
[Haxby et al. 2001]

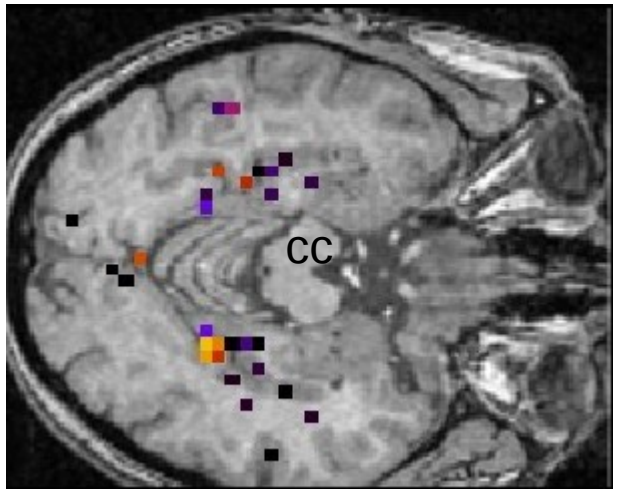
Discussion

✔ SVM and sparse models **less** powerful than univariate methods for recovery.

✔ Sparsity + clustering + randomization: good recovery

⇒ Multivariate brain mapping

✗ High computational cost (parameter setting)



Tailored priors for brain activity decoding

- Relevant priors: smoothness, sparsity, analysis sparsity
- Engineering of penalized regression models

Regularization framework

w = the discriminative pattern

Constrain w to select few parameters that explain well the data.

→ Penalized regression

$$\hat{\mathbf{w}} = \text{argmin}_{\mathbf{w}} \mathcal{L}(\mathbf{y}, \mathbf{X}, \mathbf{w}) + \alpha \mathcal{R}(\mathbf{w})$$

- L(y, X,w) is the *loss function*
- αR(w) is the **penalization** term, α > 0

$\alpha\mathcal{R}(\mathbf{w}) = \alpha\|\mathbf{w}\|^2$		Ridge (no sparsity)
$\alpha\mathcal{R}(\mathbf{w}) = \alpha\|\mathbf{w}\|_1$		Lasso (very sparse)
$\alpha\mathcal{R}(\mathbf{w}) = \alpha\left(\rho\|\mathbf{w}\|_1 + (1-\rho)\|\mathbf{w}\|^2\right)$		Elastic net (sparsity + grouping)
$\alpha\mathcal{R}(\mathbf{w}) = \alpha\left(\rho\|\mathbf{w}\|_1 + (1-\rho)\|\nabla\mathbf{w}\|^2\right)$		Smooth lasso (sparsity + smoothness)
$\alpha\mathcal{R}(\mathbf{w}) = \alpha\left(\rho\|\mathbf{w}\|_1 + (1-\rho)\|\nabla\mathbf{w}\|_{2,1}\right)$		Total variation (piecewise sparsity)

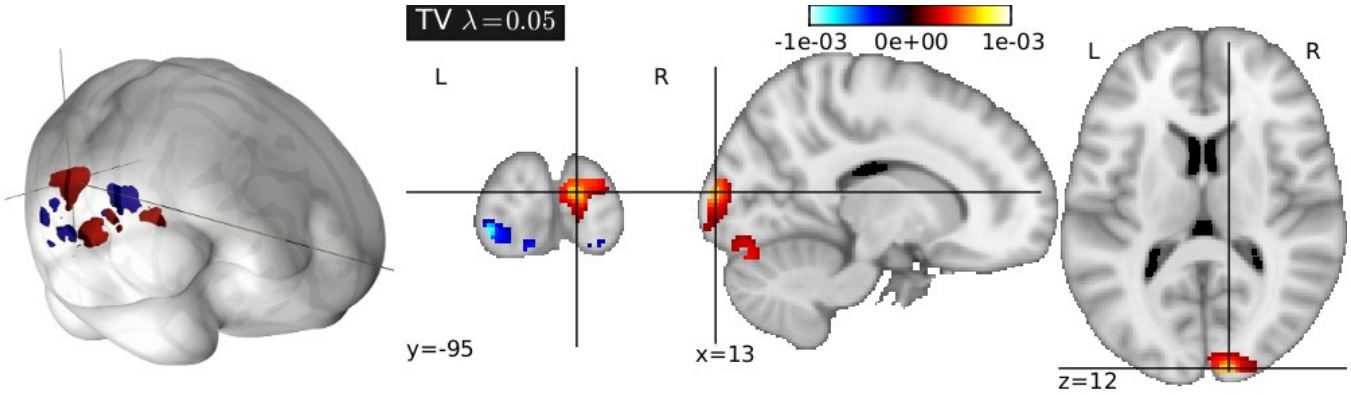
Priors and penalization: Brain decoding = engineering problem ?

Prior on the relevant activation maps

Penalization in regularized regression

Design of a norm $\|w\|$ to be minimized

Example: Total Variation penalization [Michel et al. 2011]

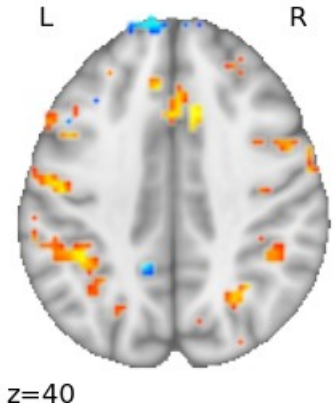


Do we need to bother about sparsity ?

Is brain activation (connectivity,..) “sparse” ? No !
But...

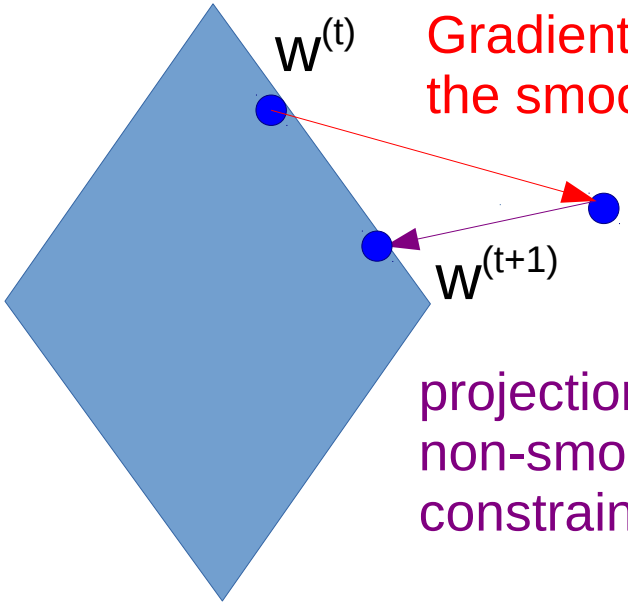
In neuroscience, people estimate discriminative patterns that look like:

But in a neuroimaging article, it will look more like



If you want to show the truly discriminative pattern, you need it to be sparse !

Solution: (F)ISTA



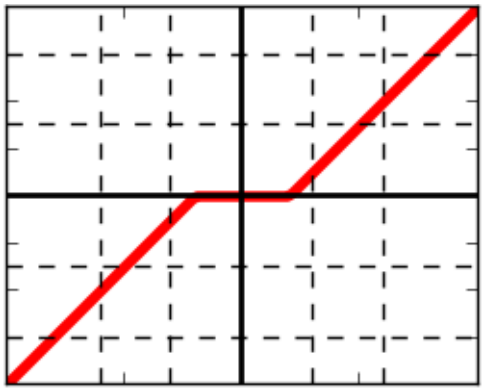
Gradient descent on the smooth terms

$$\mathbf{w}^{t+1} = \text{prox}_{\alpha\mathcal{R}}(\mathbf{w}^t - \frac{1}{L}\nabla\mathcal{L}(\mathbf{w}^t))$$

$$\text{prox}_{\alpha\mathcal{R}}(\mathbf{w}) = \text{argmin}_w \|\mathbf{w} - w\|^2 + \alpha\mathcal{R}(w)$$

projection on the non-smooth constrains

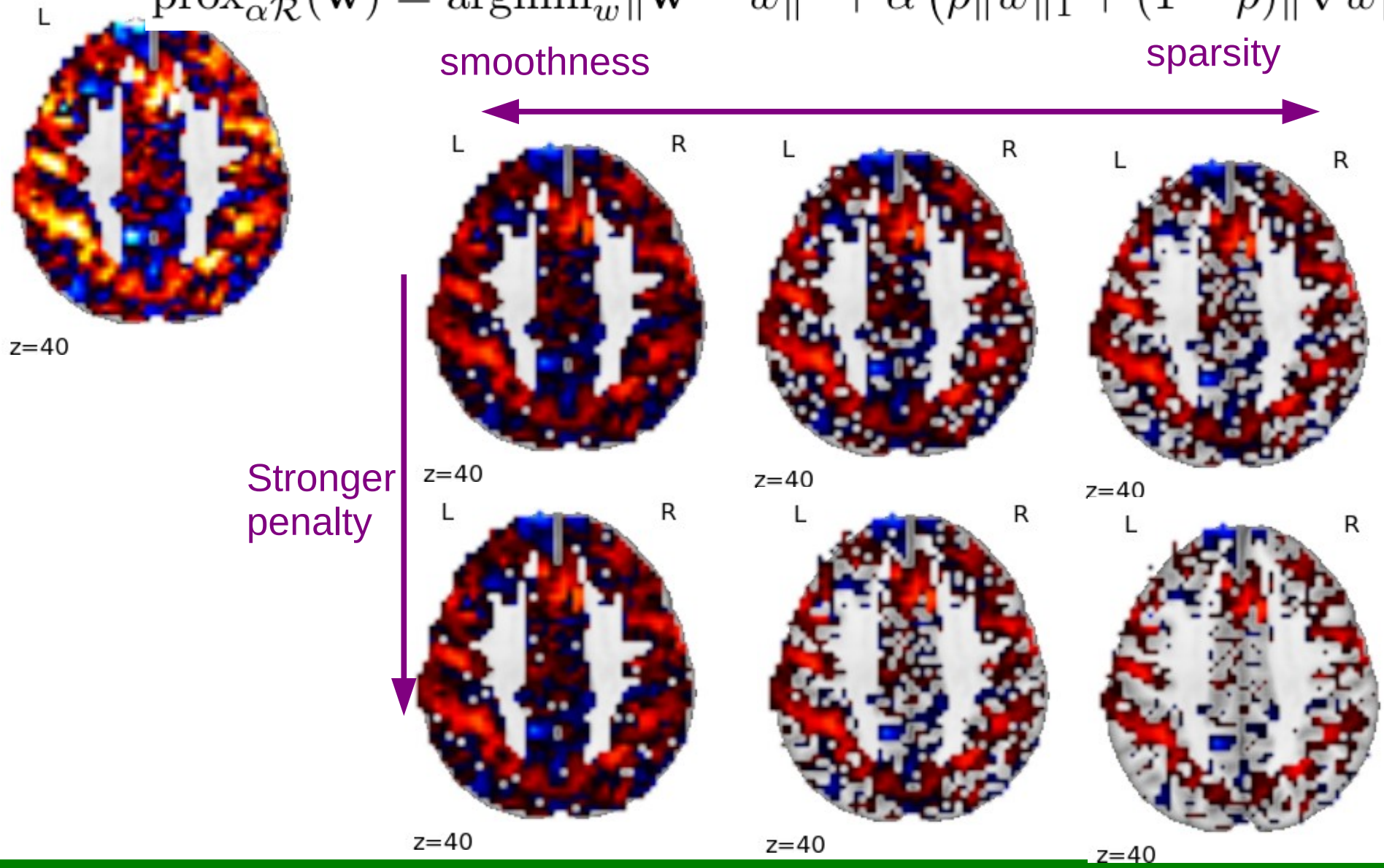
Lasso: the proximal operator is simply soft-threshodling



FISTA = accelerated ISTA (much faster convergence)

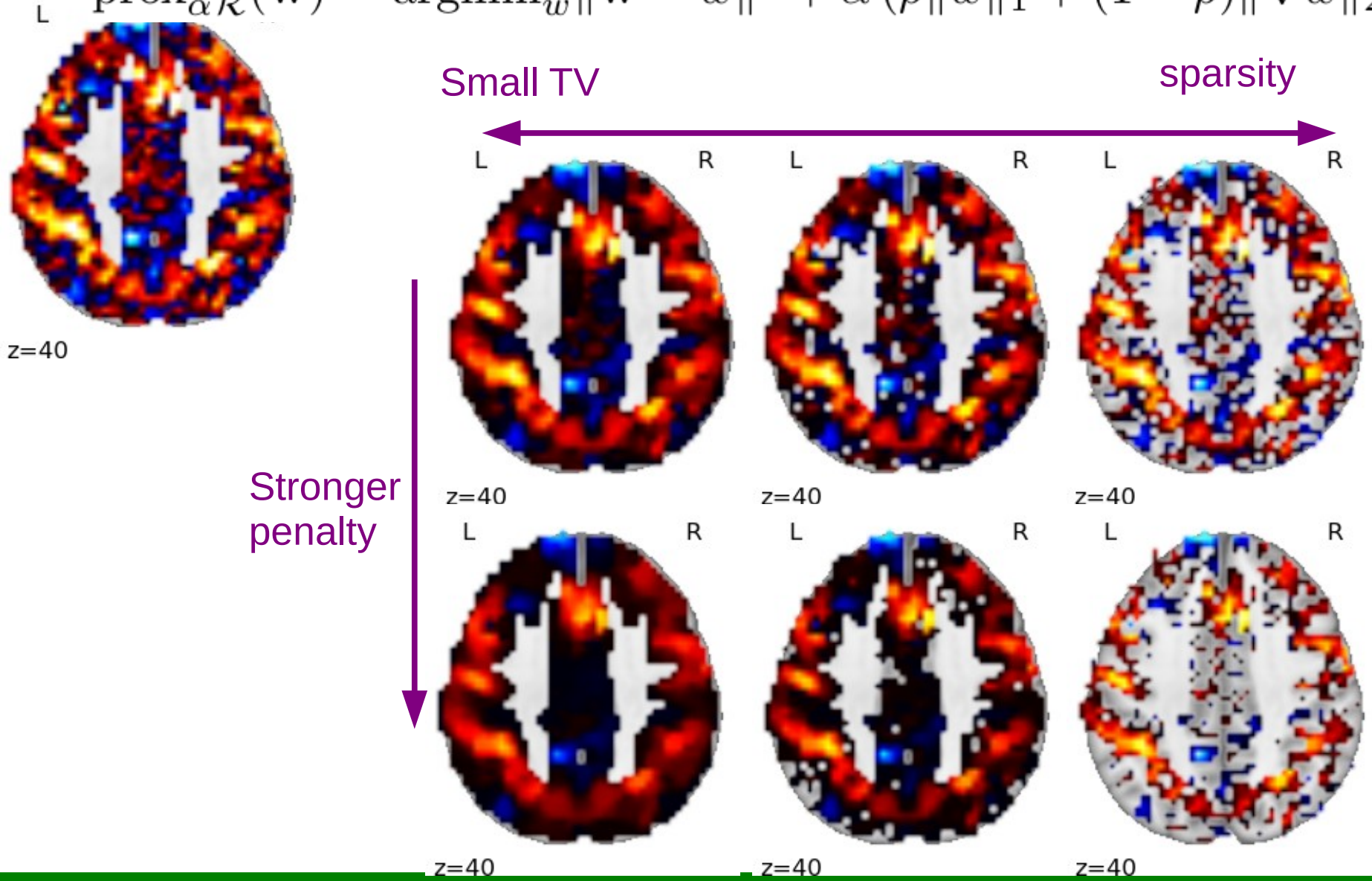
Smooth lasso: the proximal operator

$$\mathrm{prox}_{\alpha\mathcal{R}}(\mathbf{w}) = \mathrm{argmin}_w \|\mathbf{w} - w\|^2 + \alpha\left(\rho\|w\|_1 + (1-\rho)\|\nabla w\|^2\right)$$



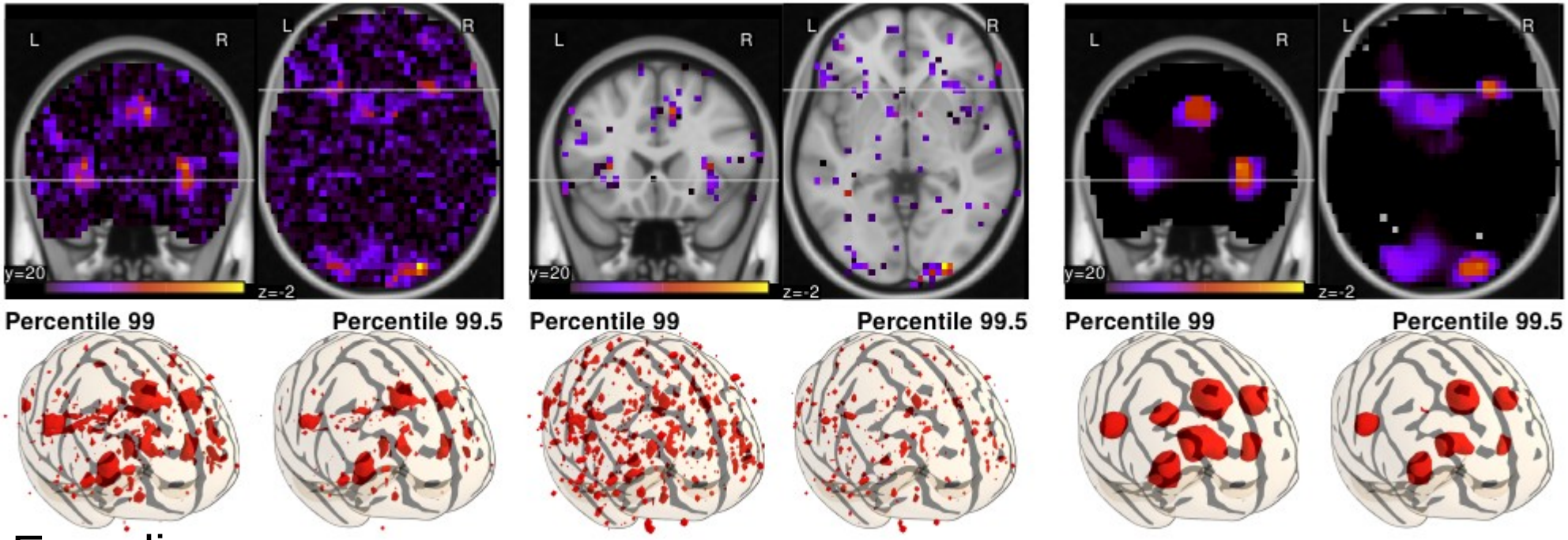
Sparse total variation: proximal operator

$$\text{prox}_{\alpha\mathcal{R}}(\mathbf{w}) = \text{argmin}_w \|\mathbf{w} - w\|^2 + \alpha\left(\rho\|w\|_1 + (1-\rho)\|\nabla w\|_{2,1}\right)$$



Example on real data

Can nevertheless be improved with adapted techniques



Encoding

Elastic net decoding

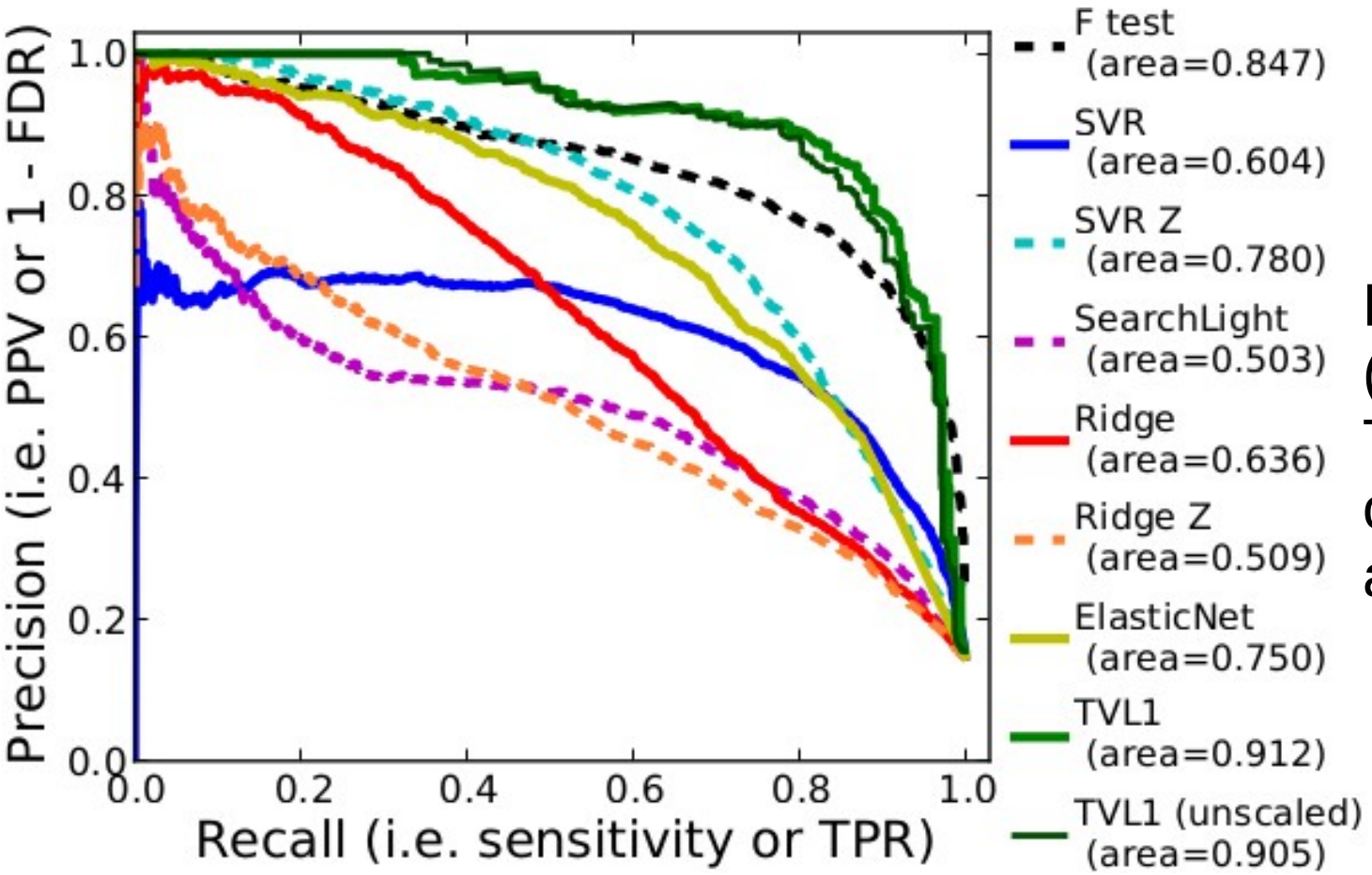
Sparse flat decoding

$$\min_{\mathbf{w}} (\mathbf{y} - \mathbf{X}\mathbf{w})^2 + \alpha \left(\rho \|\mathbf{w}\|_1 + (1-\rho)\|\mathbf{w}\|^2\right)$$

$$\min_{\mathbf{w}} (\mathbf{y} - \mathbf{X}\mathbf{w})^2 + \alpha \left(\rho \|\mathbf{w}\|_1 + (1-\rho)\|\nabla\mathbf{w}\|_{2,1}\right)$$

[Gramfort et al PRNI 2013]

Performance on recovery (simulation)



Example of recovery (simulated data): The TV-l1 prior outperforms alternatives

Discussion

- Do not try to implement these methods if not necessary. Technical issues [Dohmatob et al. PRNI 2015]
- Bayesian alternatives (ARD, smooth ARD) [Sabuncu et al.TMI 2012]
  - You lose the convexity
  - Empirical Bayes: adapts well to new data
- Cost of these methods
  - Convergence monitoring is hard
  - Smoothing + ANOVA selection + SVM is a good competitor...

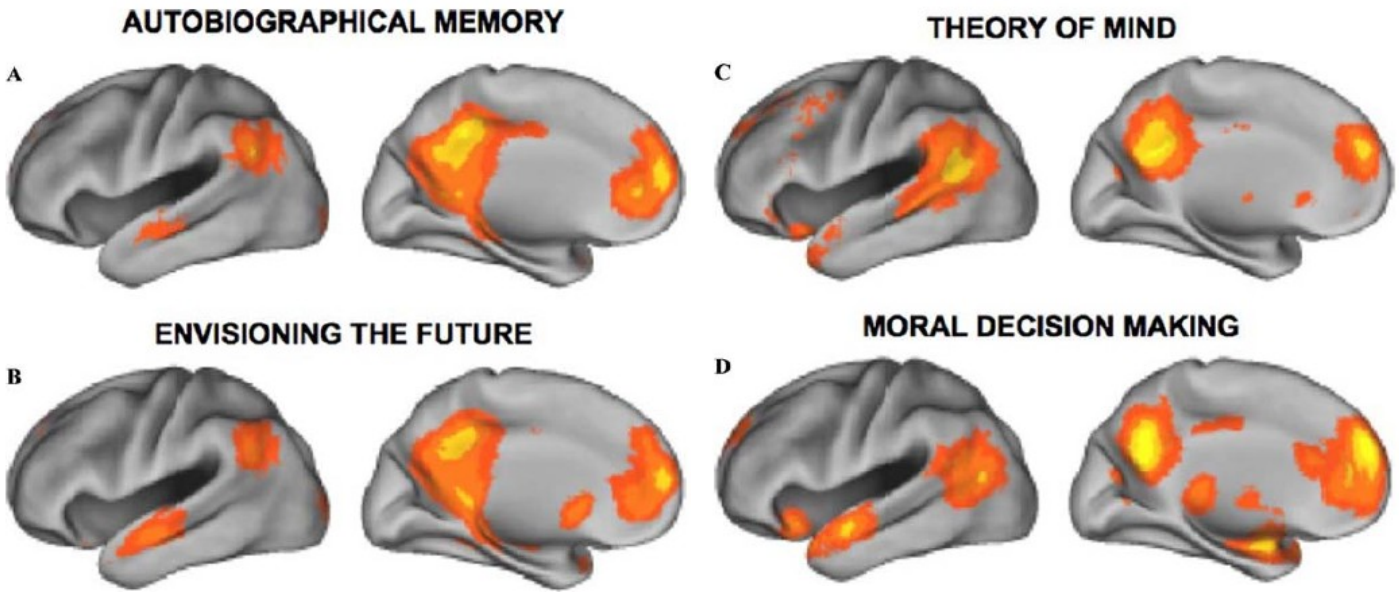
Toward Big data in cognitive neuroimaging

- Multi-label problems in cognitive neuroimaging: meta-analyses
- Mapping terms to activation maps
- Major bottlenecks

Multi-class classification is not the right setting for brain mapping

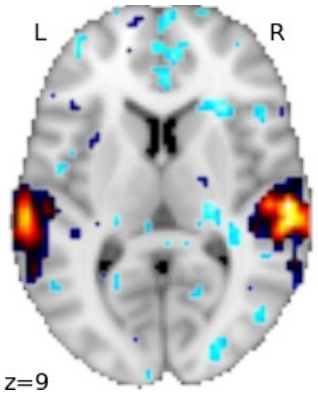
- Important questions pending....

  – Functional degeneracy between cognition and function



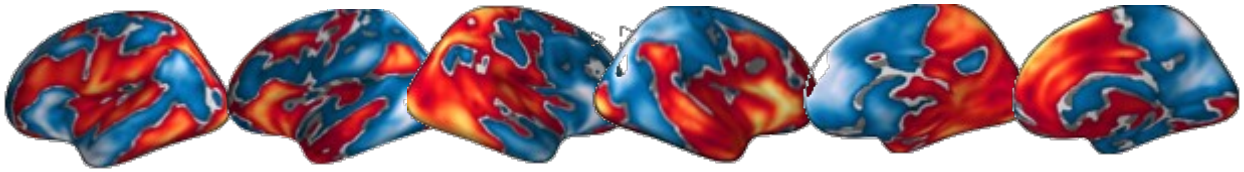
- What is this brain doing?

?



General concept

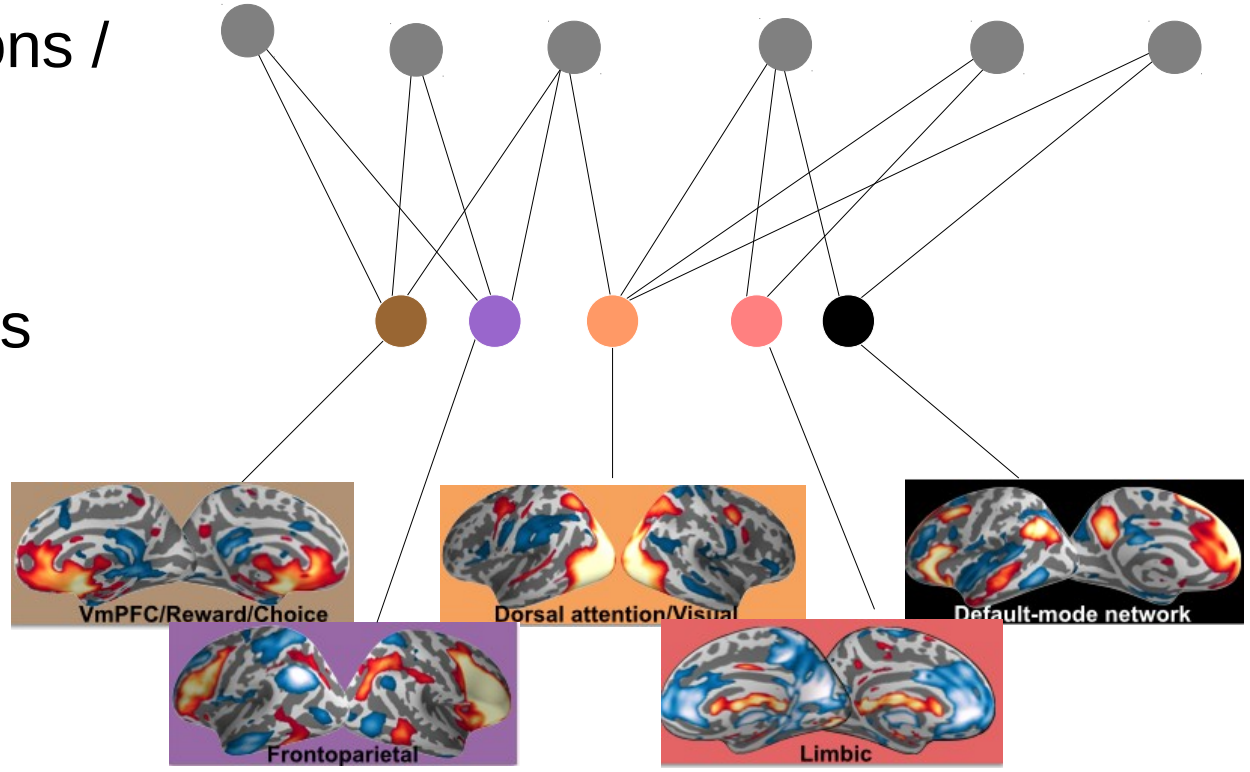
Observed SPMs



Experimental conditions /
Functional contrasts

Cognitive components

Activation patterns



Encoding

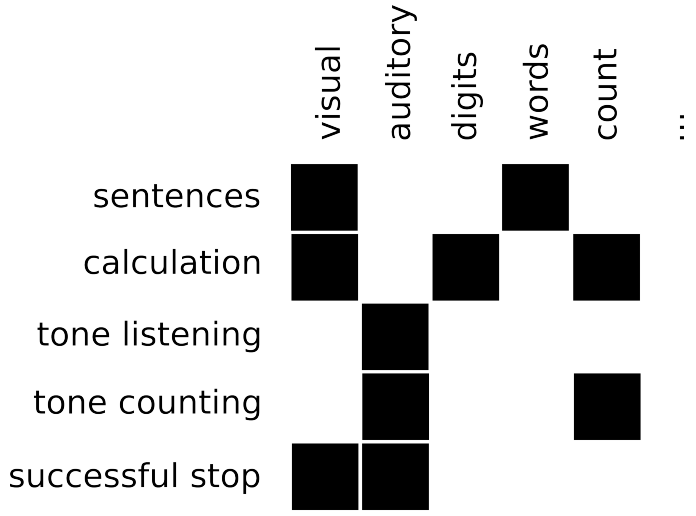
Across experiments what brain response to symbols ?

Which regions are recruited by tasks containing a given term?

- General Linear Model (GLM) for terms effects

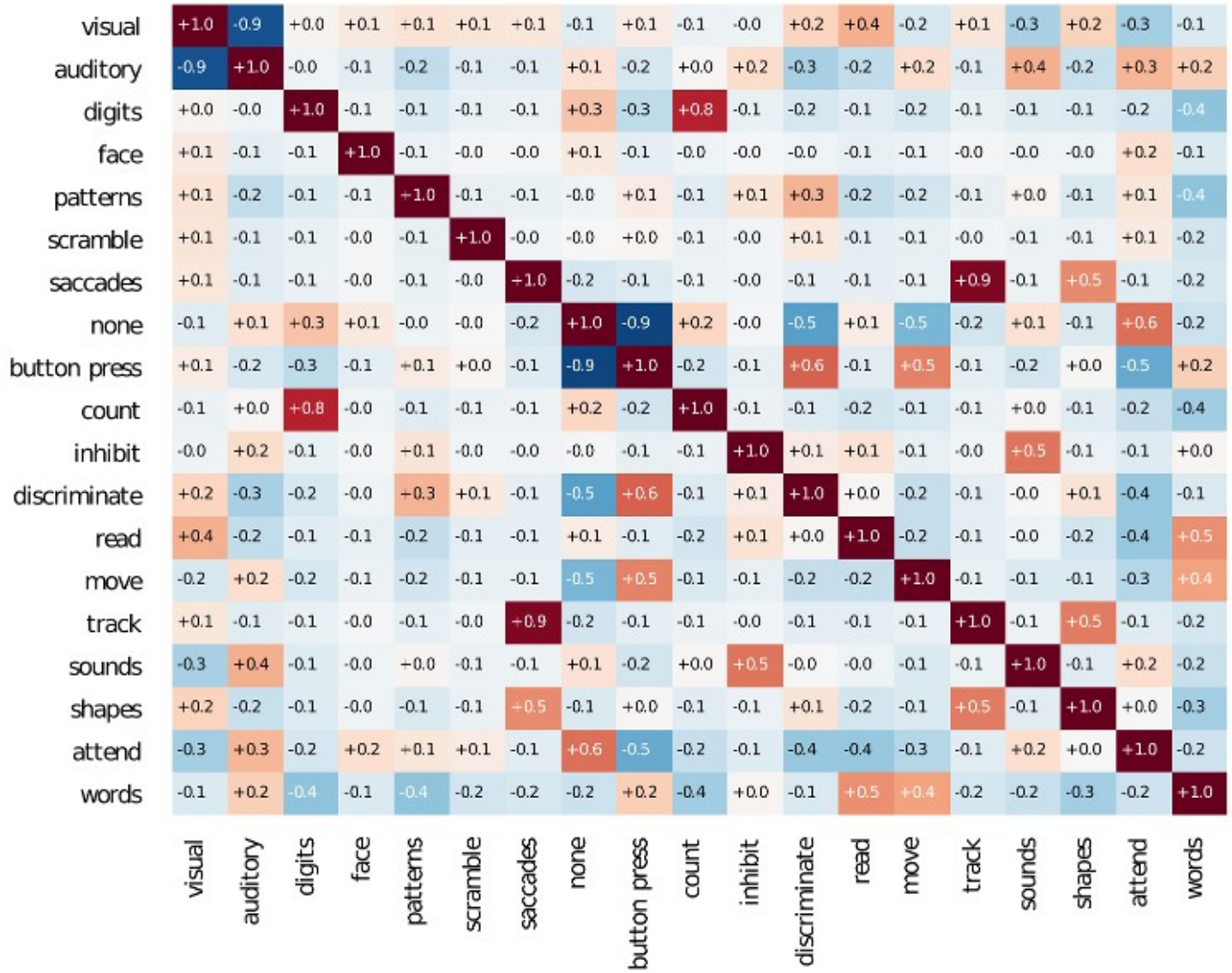
$$x = Y\beta + \varepsilon$$

x	Conditions images
Y	Design matrix
β	Terms effect
ε	Error

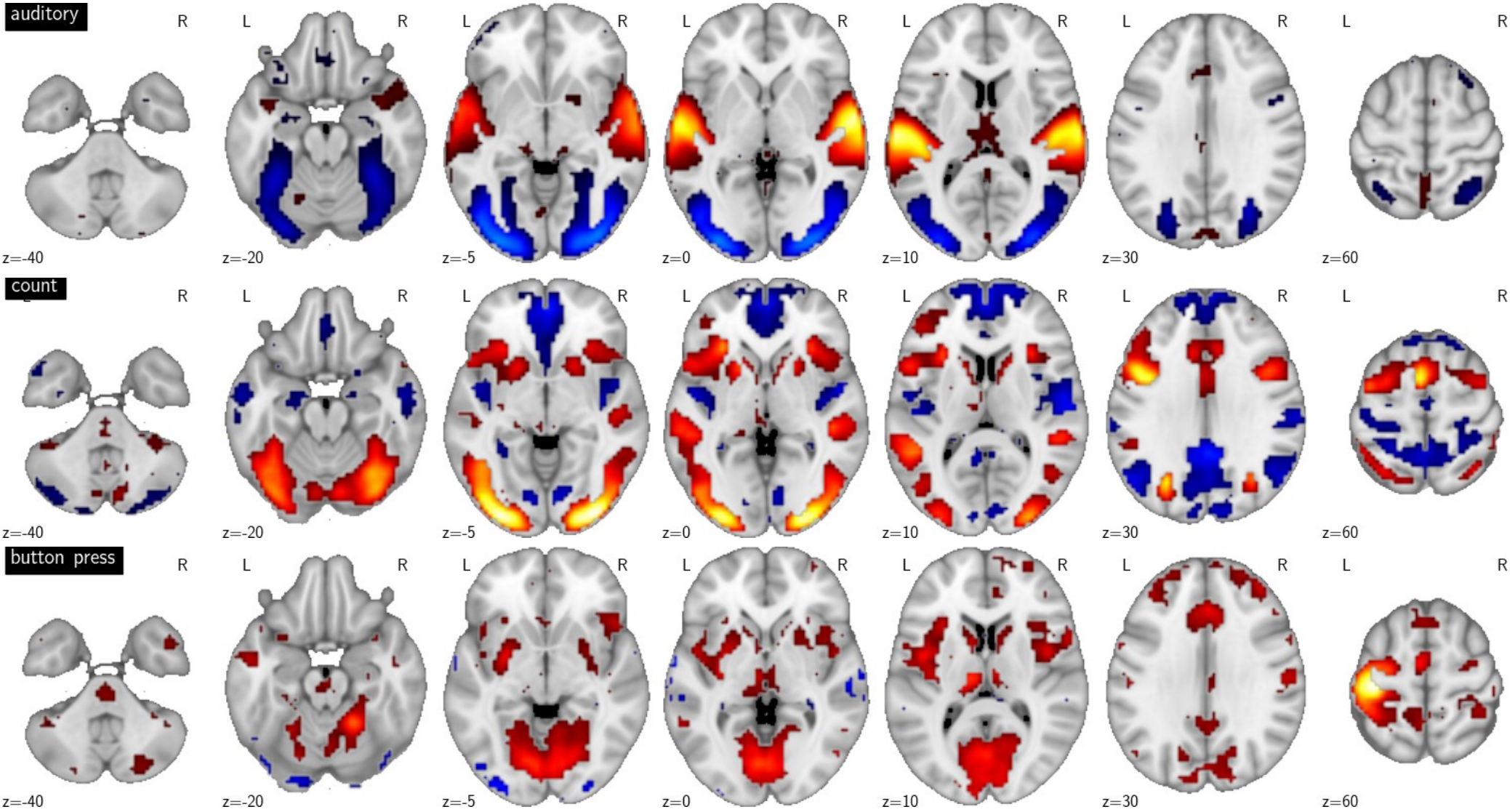


Pb with encoding approach

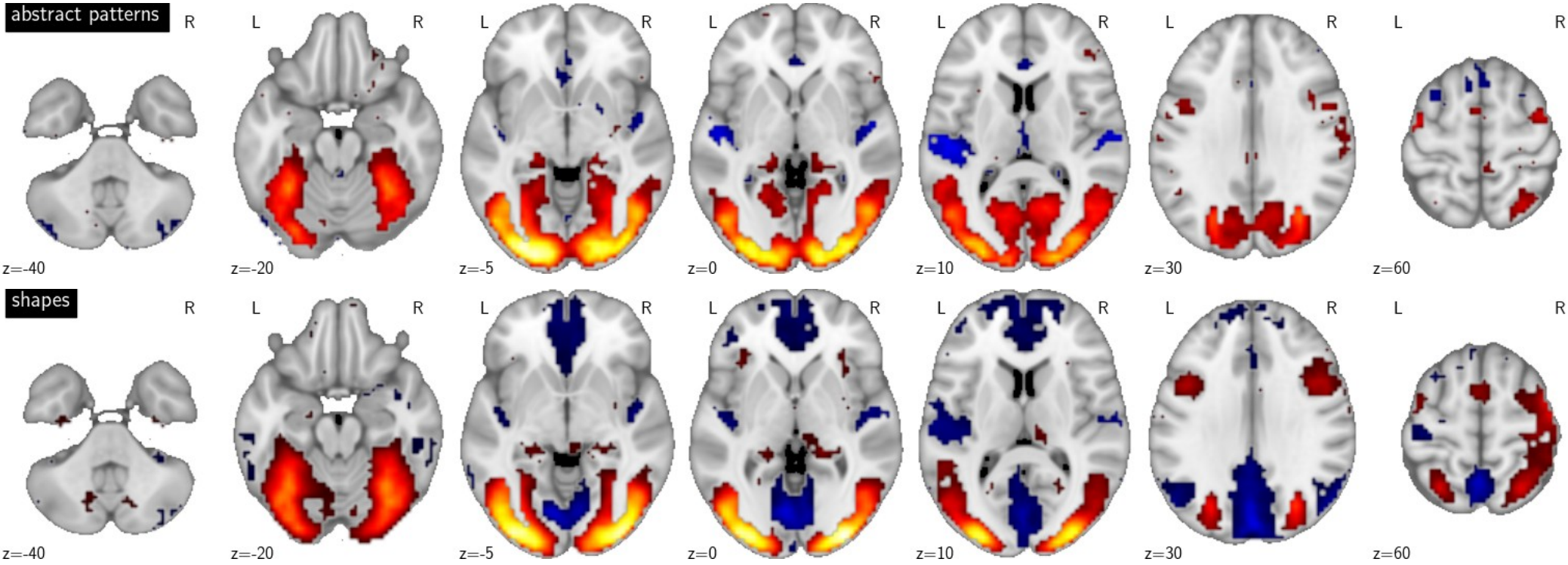
Correlation of the design matrix: difficulties from the heavily correlated terms (database bias)



Results



Results


abstract patterns
R
L
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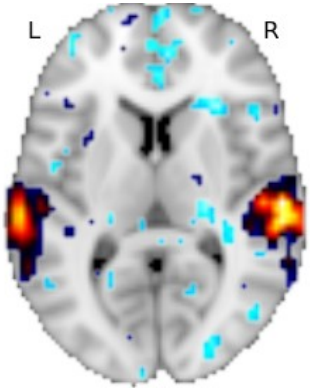
R
L
R
z=-40
z=-20
z=-5
z=0
z=10
z=30
z=60
shapes
R
L
R
L
R
L
R
L
R
L
R
L
R
z=-40
z=-20
z=-5
z=0
z=10
z=30
z=60

Decoding / Reverse inference

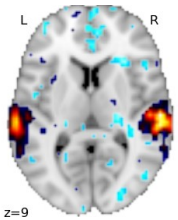
?



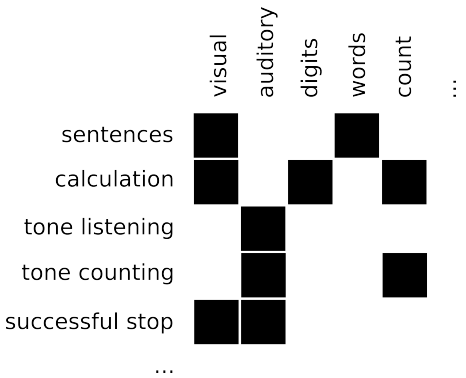
What is this brain doing?

Which regions are predictive of tasks containing a given term?

- **Multilabel** classification problem
  - more than one class may be associated with each sample
- Predict cognitive terms



Data: experimental condition images

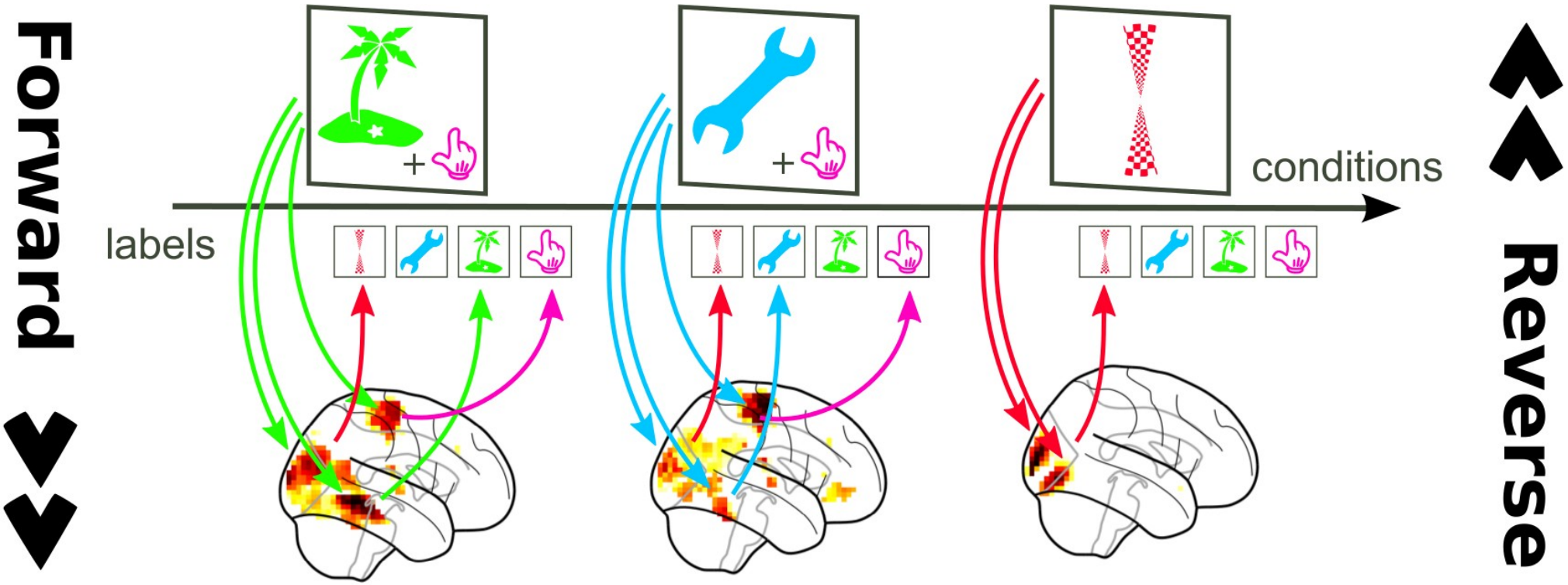


Target

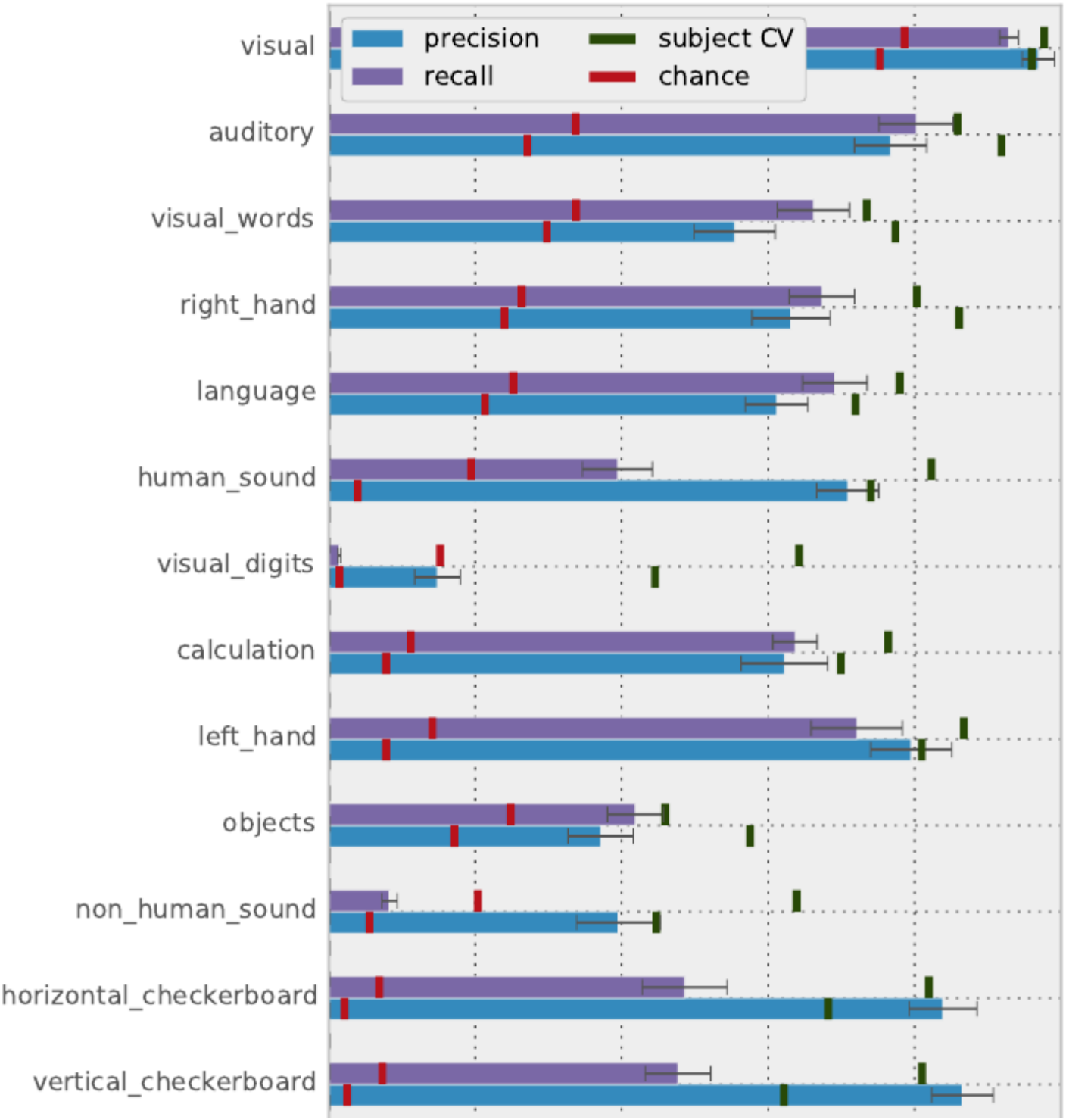
Decoding

- Problems
  - Class distribution (imbalance & covariate shift)
  - Long tailed distribution of terms
  - Standard recovery issues; noisy patterns
- Improving learning procedure
  - **Two-step** learning: discriminative sub-space selection, then prediction
  - Dimension reduction: feature clustering & Anova.
- Cross validation
  - **Leave-one study out**
  - Predict unseen conditions

Method summary



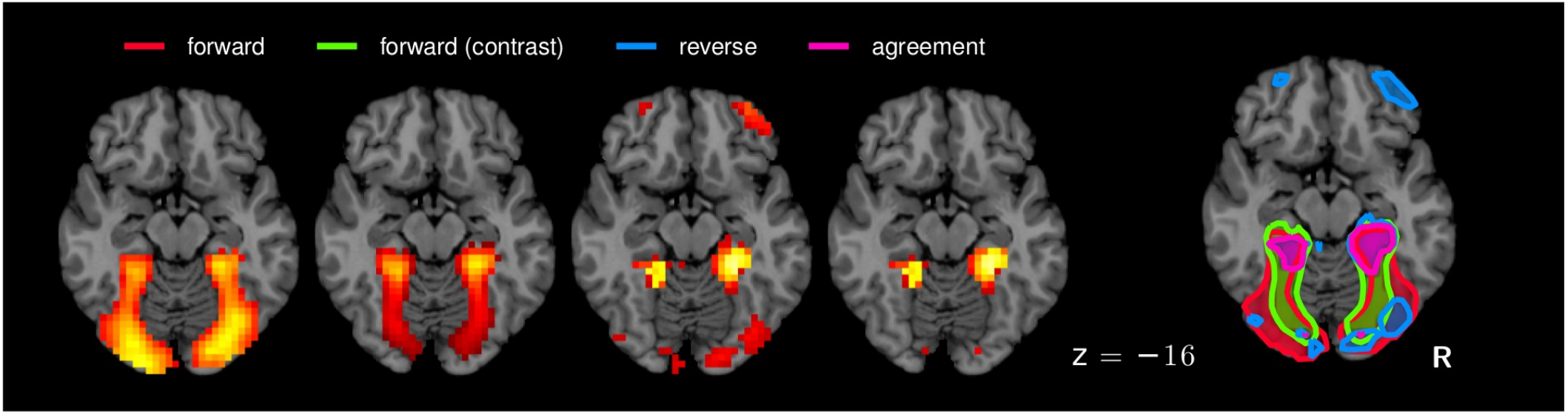
[Schwartz et al. NIPS 2013]



Precision: does not label as positive a sample that is negative

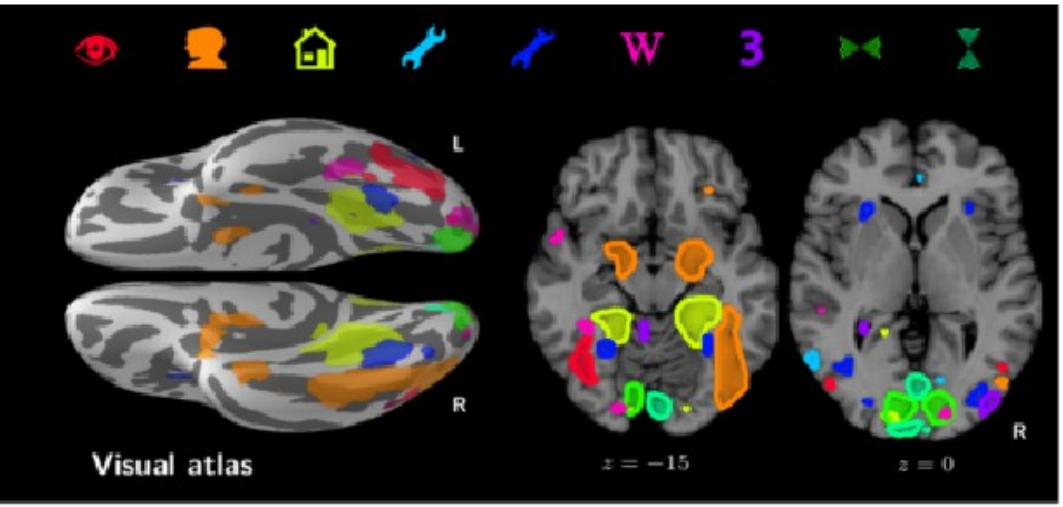
Recall: finds all the positive samples

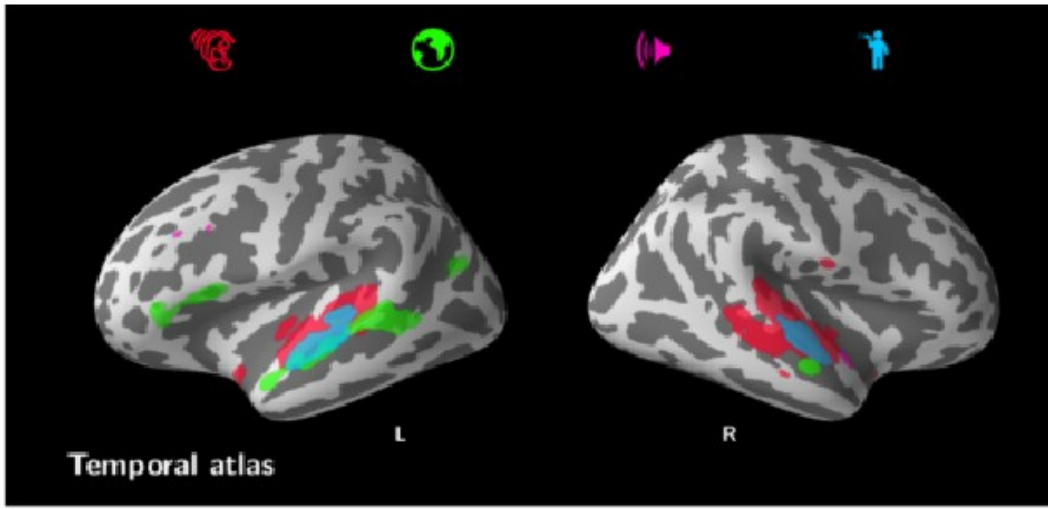
Forward and reverse inference

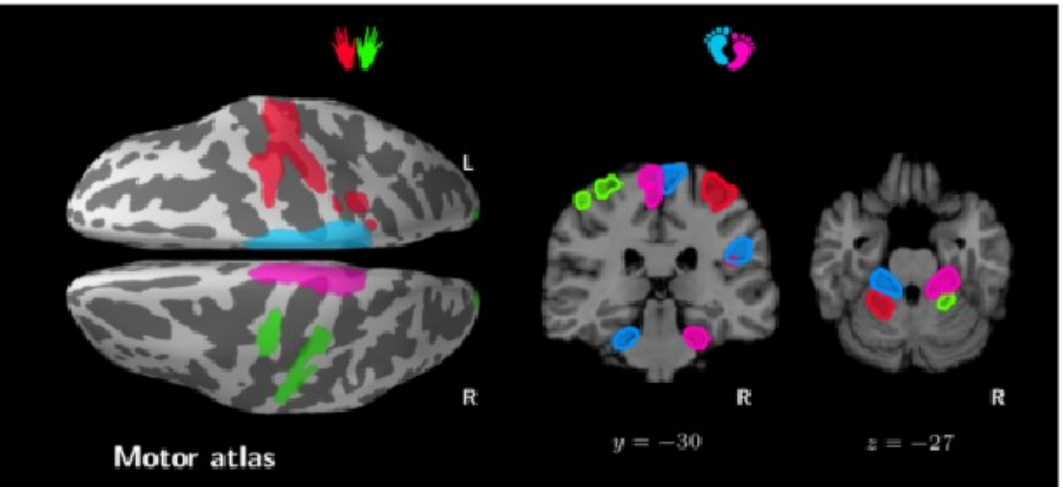


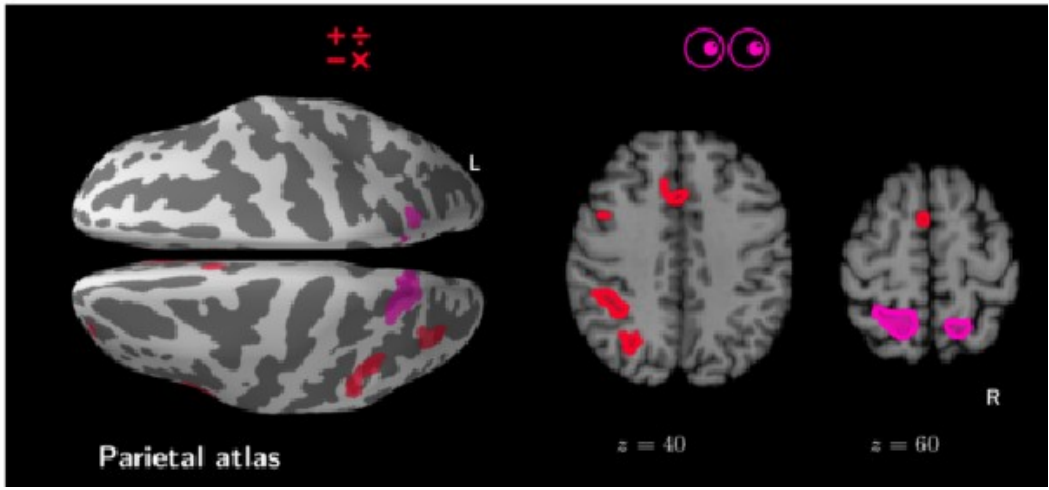
“Place”

Cognitive brain atlases









[Schwartz et al. in prep]

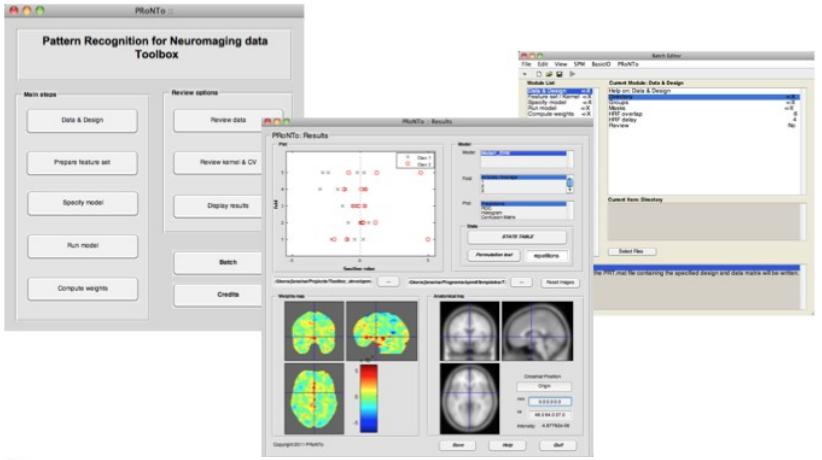
Computational bottlenecks

- Obvious limitation atm = number of training images
  - OpenfMRI and Neurovault developing fast.
- But the data handling cost. If one image = 1MB
  - 10^4 images = 10GB
  - 10^5 images = 100 GB
  - 10^6 images = 1TB
  - Moreover the resolution increases !
- Need fast learner, data compression, online training procedures. The bottleneck is memory.

[Varoquaux et al. IPMI 2013, Thirion et al. Subm.]

Available resources

Pattern Recognition for Neuroimaging Toolbox (PRoNTo)



PyMVPA: Multivariate Pattern Analysis in Python

Nilearn: Machine learning for functional neuroimaging

General Conclusions

- Look at what you do: black box models are not useful
- ML is nothing but multivariate estimation
- You probably need more data
- Do not reinvent the wheel: Pronto, PyMVPA, Nilearn
- Some topics not covered here:
  - covariance estimation (e.g. functional connectivity)
  - unsupervised models (ICA, dictionary learning...)
  - Representational similarity analysis [Kriegeskorte et al. PNAS 2008]
  - Deep nets

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